83 Parkinson Disease

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INTRODUCTION

In 1817, James Parkinson described the major clinical motor features of what today is recognized as the symptom complex known as *parkinsonism*, manifested by any combination of six cardinal features: tremor at rest, rigidity, bradykinesia–hypokinesia, flexed posture, loss of postural reflexes, and the freezing phenomenon. At least two of these features, with at least one being either tremor at rest or bradykinesia, must be present for a clinical diagnosis of parkinsonism. The many causes of parkinsonism (Table 83.1) are divided into five categories—primary, symptomatic/secondary, Parkinson-plus syndromes, various heredodegenerative diseases in which parkinsonism is a manifestation, and parkinsonism with neurotransmitter enzyme deficit. An example of parkinsonism with dopamine enzyme deficit and a benign clinical course is the condition known as *dopa-responsive dystonia*, covered in the chapter on dystonia (see Chapter 76). Primary parkinsonism is known as *Parkinson disease* (PD), which can be sporadic or familial; it is the most common type of parkinsonism encountered by neurologists and is the second most common neurodegenerative disease after Alzheimer disease (AD). In addition to the motor features of PD, the importance of nonmotor features, ranging from fatigue, sleep, and behavioral disturbances to autonomic and sensory symptoms is increasingly appreciated as contributors to the overall disability of patients with PD.

TABLE 83.1 Classification of Major Parkinsonian Syndromes

Extrapyramidal Syndromes
• Parkinson disease—sporadic and familial
Secondary Parkinsonism
• Drug-induced: dopamine antagonists and depleters
• Hemiatrophy—hemiparkinsonism
• Hydrocephalus; normal pressure hydrocephalus
• Hypoxia

• Hypoxia
• Infectious; postencephalitic
• Metabolic; parathyroid dysfunction
• Toxin: Mn, CO, MPTP, cyanide
• Trauma
• Tumor
• Vascular; multi-infarct state
Parkinson-Plus Syndromes
• Corticobasal degeneration
• Dementia syndromes
• Alzheimer disease
• Dementia with Lewy bodies
• Frontotemporal dementia
• Lytico–Bodig (Guam parkinsonism–dementia–ALS)
• Multiple system atrophy syndromes
• Striatonigral degeneration (MSA-P)
• Shy–Drager syndrome
• Sporadic olivopontocerebellar degeneration (OPCA) (MSA-C)
• Motor neuron disease–parkinsonism
• Progressive pallidal atrophy
• Progressive supranuclear palsy (PSP)
Heredodegenerative Diseases
• Neurodegeneration with brain iron accumulation (NBIA)
• Huntington disease (Westphal variant)
• Lubag (X-linked dystonia-parkinsonism)
• Mitochondrial cytopathies with striatal necrosis
• Neuroacanthocytosis
• Wilson disease
Parkinsonism with Neurotransmitter Enzyme Deficit
• Enzymatic deficiencies of dopamine synthesis

Mn, manganese; CO, carbon monoxide; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; ALS, amyotrophic lateral sclerosis; MSA-P, multiple system atrophy with predominant parkinsonism; MSA-C, multiple system atrophy with cerebellar features.

The core biochemical pathology in parkinsonism is decreased dopaminergic neurotransmission in the basal ganglia. In most of the diseases in Table 83.1, degeneration of the nigrostriatal dopamine system results in marked loss of striatal dopamine content. In some, degeneration of the striatum with loss of dopamine receptors is present and is probably responsible for the lack of therapeutic effect by dopaminergic agents in these

disorders. Drug-induced parkinsonism is the result of blockade of dopamine receptors or depletion of dopamine storage. It is not known how hydrocephalus or abnormal calcium metabolism produces parkinsonism. Physiologically, the decreased dopaminergic activity in the striatum leads to abnormal activities of the subthalamic nucleus and the globus pallidus interna (GPi), which is the predominant efferent nucleus in the basal ganglia. Understanding the biochemical pathology led to dopamine replacement therapy; understanding the physiologic change in brain network circuitry led to surgical interventions, such as deep brain stimulation of GPi, the subthalamic nucleus and ventrointermediate nucleus of the thalamus. Lesioning of these nuclei (pallidotomy, thalamotomy) is an alternative surgical technique. In addition, nondopaminergic system deficit is associated with many of the nonmotor symptoms.

EPIDEMIOLOGY

PD makes up approximately 80% of cases of parkinsonism listed in Table 83.1. The incidence and prevalence of PD increase with age. The mean age at onset is about 60 years. Onset at younger than 20 years is known as *juvenile parkinsonism*. Many cases are due to mutations in the *PRKN* gene, an autosomal recessive disorder without Lewy bodies in the degenerating substantia nigra. Some heredodegenerative diseases such as Huntington disease and Wilson disease can present as juvenile parkinsonism. Onset of primary parkinsonism between 20 and 40 years is defined as *young-onset PD*; some investigators extend the age to 50 years to account for higher genetic contribution than later onset cases. PD is more common in men, with a male-to-female ratio of 3:2. The prevalence of PD is approximately 160 per 100,000, and the incidence is about 20 per 100,000 per year. The prevalence and incidence increase exponentially with age, and at age 70 years, the prevalence is approximately 550 per 100,000, and the incidence is 120 per 100,000 per year.

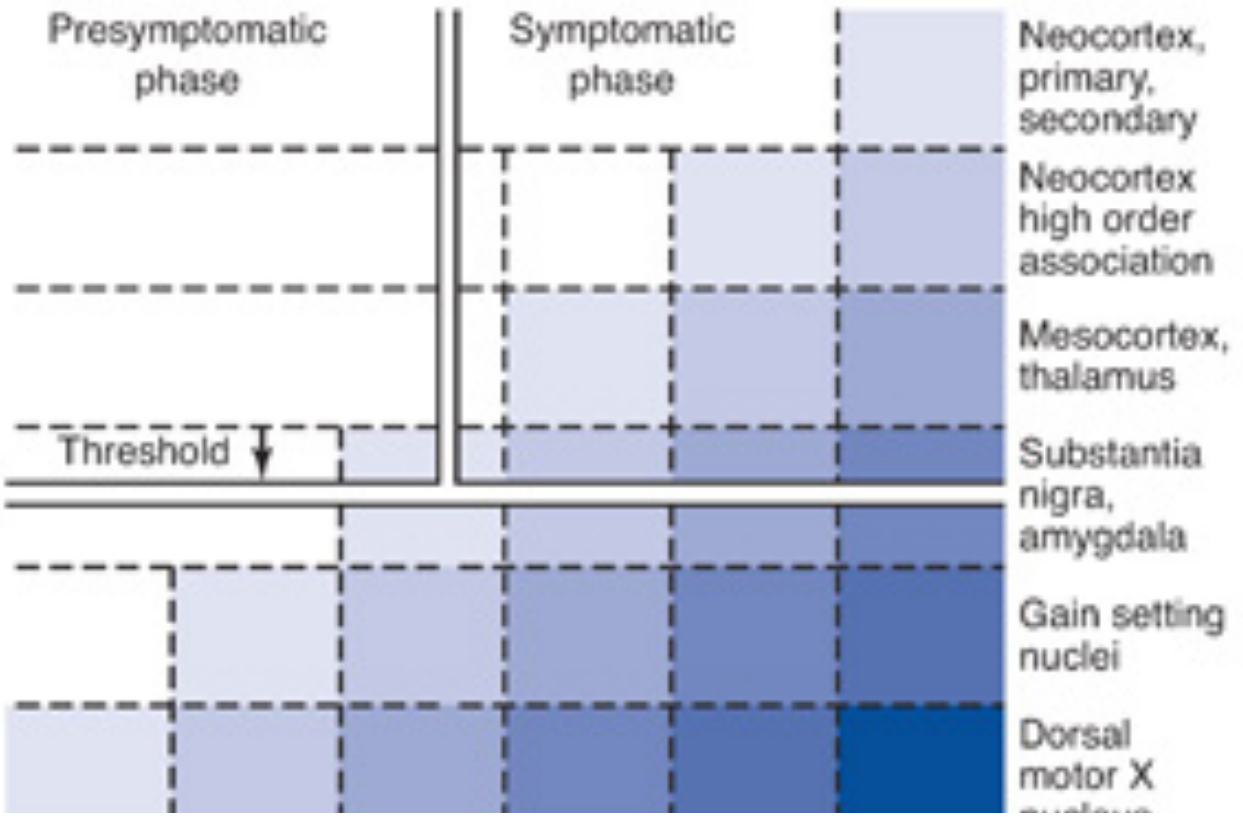
PATHOBIOLOGY

PATHOLOGY

The pathology of PD is distinctive. Degeneration of the neuromelanin-containing neurons in the brain stem occurs, especially dopamine-containing neurons in the ventral tier of the pars compacta in the substantia nigra and in the noradrenergic-containing neurons in the locus ceruleus; many of the surviving neurons in these nuclei contain eosinophilic cytoplasmic proteinaceous inclusions known as *Lewy bodies*, the pathologic hallmark of the disease. The nigral dopaminergic neurons project to the neostriatum (nigrostriatal pathway). By the time symptoms appear, the substantia nigra already has lost about 60% of dopaminergic neurons and the dopamine content in the striatum is about 80% less than

normal. Incidental Lewy bodies seen at neuropathologic examination in individuals without PD symptoms or signs are thought to represent presymptomatic individuals who would have ultimately developed clinical manifestations of PD. Lewy bodies and Lewy neurites (intra-axonal aggregates) contain the protein, α-synuclein, and are present both in PD and dementia with Lewy bodies, which is associated with wide spread cortical pathology. Other synucleinopathies include multiple system atrophy (MSA) with oligodendrocyte inclusions containing α-synuclein and some forms of neurodegeneration with brain iron accumulation (NBIA), which shows axonal spheroids with α-synuclein deposition.

Staining for Lewy bodies and neurites with antibodies to α-synuclein indicates that the aggregation of α-synuclein first occurs in the olfactory apparatus and in the caudal brain stem, especially the dorsal motor nucleus of the vagus in the medulla even in cases without involvement of substantia nigra pars compacta or clinical PD symptoms. Braak proposed a staging system for PD pathology and proposed a hypothesis that the Lewy-related pathology progressively spread rostrally up the brain stem and then into the telencephalon and cerebral cortex (Fig. 83.1). However, Lewy pathology does not correlate with actual cell loss or function and there are many cases that do not fit the pattern of hypothesized progression. The susceptible neurons containing Lewy neurites belong to the class of projection neurons with an axon that is disproportionately long, thin, and poorly myelinated or unmyelinated.



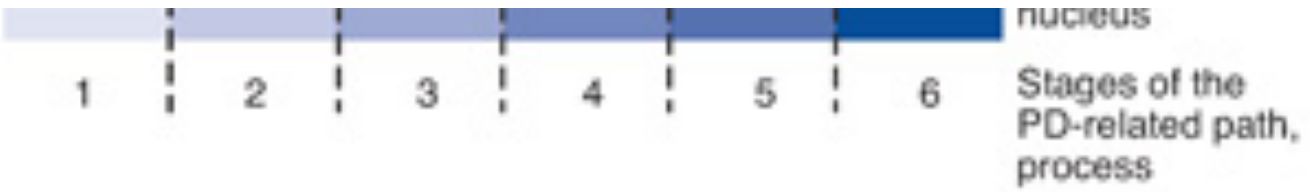


FIGURE 83.1 Six stages of PD based on distribution of Lewy neurites in the brain. Staining for α-synuclein in Lewy neurites reveals their distribution. The *darkest color* represents the most intense deposition of Lewy neurites and their earliest appearance, which is in the olfactory tubercle and dorsal motor nucleus of the vagus. The substantia nigra develops Lewy neurites at stage 3, following which symptoms of PD appear (Braak stage 4). The neocortex is involved in stages 5 and 6. The susceptible neurons belong to the class of projection neurons with an axon that is disproportionately long, thin, and poorly myelinated or unmyelinated. (From Braak H, Bohl JR, Müller CM, et al. Stanley Fahn lecture 2005: the staging procedure for the inclusion body pathology associated with sporadic Parkinson's disease reconsidered. *Mov Disord*. 2006;21[12]:2042–2051.)

ETIOLOGY

The cause of PD in the vast majority of patients is unknown. Research has discovered both environmental and genetic factors. The discovery that the chemical agent 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) can cause parkinsonism raised the possibility that PD might be caused by an environmental toxin. No single environmental factor has emerged as essential, but growing up in a rural farming environment has been disproportionately frequent in some studies, suggesting potential role of pesticides, some resembling MPTP in chemical structures. Exposure to excess levels of manganese may produce a neurobehavioral syndrome that shares some of the cognitive and motor features of PD, but whether it increases the risk of idiopathic PD is controversial. Interestingly, decreased risk of PD in those with high level of caffeine consumption or cigarette smoking has been consistently noted. High uric acid levels are also associated with decreased risk and slower progression of PD.

GENETICS

Contribution of genetic factors has been recognized only since late 1990s. Studies of twins showed that onset of PD before age 50 years has a higher likelihood of a genetic cause. The first genetic form of PD was discovered in 1997 and now more than 20 different genetic forms of parkinsonism, labeled as PARK, have been discovered. Many of them are Parkinson-plus syndromes, and pathology is variable including some without Lewy body and some as NBIAs. These are summarized in Table 83.2. We will discuss well-established genetic forms with typical PD clinical phenotypes here.

TABLE 83.2 The Most Definitive Genetic Forms of Parkinson Disease

Name and Locus	Gene	Mode of Inheritance	Pathologic and Clinical Features	Protein Function	Where Found
PARK1 and 4 4q22.1	*SCNA*	Autosomal dominant	Lewy bodies; earlier onset and more aggressive course; L-dopa–responsive parkinsonism, dementia, hallucinations, autonomic dysfunction	*α-Synuclein* possibly synaptic vesicle trafficking, elevated in bird song learning	Families in Germany, Italy, United States (Contoursi kindred), Greece, Spain
PARK8 12q12	*LRRK2*	Autosomal dominant	Pathologic pleomorphism; indistinguishable from idiopathic PD		Worldwide
PARK2 6q26	*PRKN*	Autosomal recessive	Often juvenile onset without Lewy bodies; slowly progressive; no dementia	Parkin, a ubiquitin E3 ligase, attaches short ubiquitin peptide chains to a range of proteins, likely to mark degradation; supports mitophagy	Ubiquitous, originally in Japan, very common in juvenile onset
PARK6 1p36.12	*PINK-1*	Autosomal recessive	Juvenile onset	Mitochondrial kinase, modulates mitochondrial dynamics; supports mitophagy	Families in Italy, Spain, Philippines, Taiwan, Israel, Japan, Ireland, and North America
PARK7 1p36.23	*DJ-1*	Autosomal recessive	Early onset	Possible atypical peroxiredoxin and may play a role in apoptosis	Families in Holland, Italy, Uruguay
Glucocerebrosidase 1q22	*GBA*	Autosomal dominant; susceptibility gene; low penetrance; most common genetic risk factor gene	Indistinguishable from idiopathic PD	Lysosomal enzyme	About 13% of sporadic PD in Ashkenazi Jews, found in all ethnic groups

PD, Parkinson disease.

The first genetic cause of PD (PARK1) was discovered to be mutations in *SNCA* gene located on chromosome 4q22.1 coding for the protein *α*-synuclein. *α*-Synuclein is an abundant presynaptic protein. The resulting parkinsonism transmits in an autosomal dominant pattern. It is rare, being reported only in a small number of families originating in Greece, Italy, Germany, and Spain. However, single nucleotide polymorphisms have been associated with sporadic PD and the protein *α*-synuclein is present in Lewy bodies, even in patients with PD without genetic mutations, suggesting potential pathophysiologic role of *α*-synuclein in sporadic form of PD. It is not known if Lewy bodies contribute to neuronal degeneration or are a protective mechanism to slow neuronal death. Duplication and triplication of the *α*-synuclein gene also cause familial parkinsonism (PARK4), suggesting that overexpression of the normal (wild-type) protein suffices to provoke dopaminergic neurodegeneration.

Another gene defect causing familial PD is PARK8, which has been mapped to chromosome 12q12 and encodes for a previously unknown protein named *leucine-rich repeat kinase-2* (LRRK2), also known as *dardarin*. This 2527 amino acid protein belongs to the family of the ROCO protein, contains a protein kinase domain, and is ubiquitously expressed in the central nervous system (CNS). About a dozen pathogenic *LRRK2* mutations have been identified, which have been found to be the most frequent genetic cause of PD, accounting to up to 5% of familial cases in the Caucasian population. Some ethnic groups have a particularly high prevalence; the most common mutation, G2019S, has an increased frequency among Ashkenazi Jews (18.3% of those with PD) and North African Berbers (39% of those with PD). *LRRK2* mutations result in an autosomal dominant parkinsonism that resembles late-onset idiopathic PD. Genome-wide association studies have shown significance of *LRRK2* polymorphism in sporadic PD as well. Although the neuropathology associated with *LRRK2* mutations is highly variable with some with Lewy bodies and others with neurofibrillary tangles, degeneration of substantia

nigra neurons has been observed consistently.

The most commonly occurring gene defect causing juvenile familial parkinsonism is PARK2 (*PRKN*) on chromosome 6q26, coding for the E2-dependent E3 ubiquitin-protein ligase, parkin. Mutations in the parkin gene result in an autosomal recessive parkinsonism that is slowly progressive, with onset usually before age 30 years and with sleep benefit; rest tremor can be present. This cause of PD has a better prognosis for both motor and cognitive outcomes than idiopathic PD. There is degeneration of substantia nigra neurons, but in most instances, no Lewy body inclusions are found. Some typical adult-onset PD patients have been found to have a single heterozygotic mutation of the *PRKN* gene and with Lewy bodies at autopsy. Other recessive forms with similar juvenile parkinsonism include those with PTEN-induced putative kinase 1 (*PINK1*; PARK6) and *DJ-1* (PARK7) mutations.

Glucocerebrosidase (*GBA*) gene mutations, when homozygous, cause autosomal recessive Gaucher disease. Heterozygous carriers are at increased risk for developing PD that is indistinguishable from idiopathic PD. PD patients with *GBA* mutations tend to have more cognitive problems, and about 13% of Ashkenazi Jews with PD have this mutation, but the same mutation causes PD in other ethnic groups as well.

PATHOGENESIS

Two major pathogenic hypotheses have emerged from epidemiologic and genetic evidences as well as postmortem examinations. One hypothesis proposes that mitochondrial dysfunction and oxidative stress are critical in the pathogenesis, whereas there is also evidence that misfolding and aggregation of proteins are instrumental in the PD neurodegenerative process. These two hypotheses are not mutually exclusive, and interactions among these pathogenic factors are likely to be important in understanding the mechanisms of neurodegeneration in PD.

Environmental toxins associated with PD risk can damage mitochondria and generate oxidative stress. Postmortem biochemical observations also show that complex I activity of mitochondria is reduced in substantia nigra of patients with PD. Such a defect would decrease the synthesis of ATP and also lead to the buildup of free electrons, thereby increasing oxidative stress. Substantia nigra in patients with PD shows severe depletion of reduced glutathione, the major substrate required for the elimination of reactive oxygen species. This change is also seen in brains with incidental Lewy bodies and therefore could be the one of the earliest biochemical abnormalities of PD. It is not known, however, if this change is the cause or the result of oxidative stress. Iron in the substantia nigra may also play a critical role because it can catalyze the formation of the highly reactive hydroxyl radical from hydrogen peroxide. Recessive genes such as *PRKN* and *PINK1* have been shown to have wide ranging effects on mitochondrial quality control such as regulating

mitochondria biogenesis, maintaining fission–fusion balance to remove damaged mitochondria, transport of mitochondria, and turnover of damaged mitochondria by recruiting autophagic machinery. Another recessive gene, *DJ-1* is implicated in a pathway handling oxidative stress. Endogenous factors may also predispose melanin-containing monoaminergic neurons to neurodegeneration. Cellular oxidation reactions (such as enzymatic oxidation and auto-oxidation of dopamine and other monoamines) result in the formation of reactive oxygen species such as dopamine quinone and other metabolic products that can damage the monoamine neurons. In addition, dopaminergic neurons and other susceptible neurons such as noradrenergic neurons in locus ceruleus are autonomous pacemakers and have long highly arborized axons, thereby subjected to high metabolic demands. A presence of a particular calcium channel may predispose these neurons to basal metabolic stress.

Most of the genes involved in PD seem to have multiple cellular functions. Nonetheless, genes producing recessive forms of PD have been implicated more in mitochondrial and metabolic pathways as noted earlier, whereas genes associated with autosomal dominant forms of PD have been noted to be involved in protein degradation homeostasis. Whether the hallmark of PD pathology, the Lewy body, which contains *α*-synuclein contributes to the toxicity or is a protective mechanism is not known. Evidence points to toxicity of protofibrillar forms of *α*-synuclein, and intriguing experimental evidence suggests that abnormal forms of *α*-synuclein may have the prion-like property of propagating its abnormal conformation and spreading the pathology along the neuronal projections and across the synaptic connections. *α*-Synuclein is involved in vesicle recycling. LKKR2 plays a role in vesicular trafficking and cytoskeletal function. Another PD gene, vacuolar protein sorting 35 (*VPS35*) was identified to cause autosomal dominant PD with typical features and good response to levodopa. This gene encodes a subunit of the retromer complex involved in endosomes and vesicular recycling. *α*-Synuclein and LRRK2 affects protein degradation pathways, including autophagy, a process of cell degradation of dysfunctional cellular components by lysosomes. Glucocerebrosidase is a lysosomal enzyme.

CLINICAL MANIFESTATIONS

CARDINAL MOTOR FEATURES

The clinical features of tremor, bradykinesia, rigidity, loss of postural reflexes, flexed posture, and freezing are the six cardinal motor features of parkinsonism. Not all need to be present, but at least two should be seen, either rest tremor or bradykinesia, before parkinsonism is considered clinically probable. *Rest tremor* at a frequency of 4 to 5 Hz is present in the extremities, almost always distally; occasionally, the rest tremor occurs in

the proximal part of the limb instead of distally. The classic "pill-rolling" tremor involves the thumb and forefinger. Rest tremor disappears with action but sometimes reemerges as the limbs maintain a posture (Video 83.1). Rest tremor is also common in the lips, chin, and tongue. Rest tremor of the hands increases with walking and may be an early sign when others are not yet present. Stress or excitement worsens the tremor. Some patients will have an action tremor instead of or in addition to rest tremor. The biggest differential diagnosis of parkinsonian tremor is essential tremor (ET). Ordinarily, these two causes of tremor are easy to distinguish. Tremor of PD is typically a rest tremor, whereas that of ET is a postural and action tremor. However, the manifestations of these tremors can overlap, with patients with severe ET having rest tremor. Not all patients with PD have tremor; when absent, the diagnosis is more difficult to make, and it usually takes longer after onset of symptoms to make a diagnosis. Eventually, bradykinesia worsens to the point of some disability, such as micrographia or dragging a leg when walking, that the patient seeks medical attention.

Akinesia is a paucity of spontaneous movement, but the term is often used interchangeably with *bradykinesia* and *hypokinesia*. Bradykinesia (slowness of movement, difficulty initiating movement, and loss of automatic movement) and hypokinesia (reduction in amplitude of movement, particularly with repetitive movements, so-called decrementing) are the most common features of parkinsonism, although they may appear after the tremor. Bradykinesia has many facets, depending on the affected body parts. The face loses spontaneous expression (masked facies, *hypomimia*) with decreased frequency of blinking. Poverty of spontaneous movement is characterized by loss of gesturing and by the patient's tendency to sit motionless. Speech becomes soft (*hypophonia*), and the voice has a monotonous tone with a lack of inflection (*aprosody*). Some patients do not enunciate clearly (*dysarthria*) and do not separate syllables clearly, thus running the words together (*tachyphemia*). Bradykinesia of the dominant hand results in small and slow handwriting (*micrographia*) and in difficulty shaving, brushing teeth, combing hair, buttoning, or applying makeup. Playing musical instruments is impaired. Walking is slow, with a shortened stride length and a tendency to shuffle with loss of heel strike; arm swing decreases and eventually is lost. Difficulty arising from a deep chair, getting out of automobiles, and turning in bed are symptoms of truncal/body bradykinesia. Drooling saliva results from failure to swallow spontaneously, a feature of bradykinesia, and is not caused by excessive production of saliva. The patients can swallow properly when asked to do so but only constant reminders allow them to keep swallowing saliva. Similarly, arm swing can be normal if the patient voluntarily, and with effort, wishes to have the arms swing on walking. Pronounced bradykinesia prevents a patient with parkinsonism from driving an automobile when foot movement from the accelerator to the brake pedal is too slow.

Bradykinesia is commonly misinterpreted by patients as weakness. Fatigue, a common complaint in PD, particularly in the mild stage of the disease before pronounced slowness appears, may be related to mild bradykinesia or rigidity or may be an independent feature. Subtle signs of bradykinesia can be detected even in the early stage of parkinsonism if one examines for slowness in shrugging the shoulders, lack of gesturing, decreased arm swing, and decrementing amplitude of rapid successive movements. With advancing bradykinesia, slowness and difficulty in the execution of activities of daily living increase. A meal normally consumed in 20 minutes may be only half eaten in an hour or more. Swallowing may become impaired with advancing disease, and choking and aspiration are concerns. Bradykinesia is manifested in many ways depending on the body part affected (Table 83.3).

TABLE 83.3 Clinical Signs of Bradykinesia

Cranial
• Hypomimia (masked face)
• Staring expression with decreased blinking and retracted lids
• Hypometric saccades
• Impaired convergence
• Impaired upward gaze
• Hypophonia (soft voice)
• Aprosody of speech (loss of inflection of voice)
• Palilalia (repetition of first syllable)
• Sialorrhea (drooling of saliva)
Upper Limbs
• Reduced spontaneous movement (e.g., lack of gesturing)
• Decrementing amplitude with repetitive movements of opening and closing fists, pronating and supinating the forearms, and tapping a finger on the thumb
• Micrographia and slowness with handwriting
• Slowness in cutting food, dressing, and in hygienic care
• Decreased arm swing when walking
Lower Limbs
• Decrementing amplitude with repetitive movements of

- Decrementing amplitude with repetitive movements of stomping feet or tapping toes
- Short, slow steps when walking
- Not elevating feet as high as normal when walking, tendency to shuffle
- Narrow base when walking
- Tendency to walk on toes; loss of heel strike

Body Bradykinesia

- Slowness in initiating movement on command
- Difficulty arising from a chair and turning in bed
- Difficulty carrying out two motor acts simultaneously
- Reduced shrugging of shoulders

Rigidity is an increase in muscle tone that is elicited when the examiner moves the patient's limbs, neck, or trunk. This increased resistance to passive movement is equal in all directions and usually is manifested by a ratchety "give" during the movement. This so-called cogwheeling is caused by the underlying tremor even in the absence of visible tremor. Cogwheeling also occurs in patients with ET. Rigidity of the passive limb increases while another limb is engaged in voluntary active movement ("Froment maneuver").

Flexed posture commonly begins in the arms and spreads to involve the entire body. The head is bowed; the trunk is bent forward; the back is kyphotic; the arms are held in front of the body; and the elbows, hips, and knees are flexed. Deformities of the hands include ulnar deviation of the hands, flexion of the metacarpophalangeal joints, and extension of the interphalangeal joints (striatal hand). Inversion of the feet is apparent, and the big toes may be dorsiflexed (striatal toe) and the other toes curled downward. Lateral tilting of the trunk commonly develops (Pisa syndrome), and extreme flexion of the trunk (camptocormia) is sometimes seen.

Loss of postural reflexes leads to falling and eventually to inability to stand unassisted. Postural reflexes are tested by the *pull test*, which is performed by the examiner, who stands behind the patient and gives a sudden firm pull on the shoulders after explaining the procedure and who checks for retropulsion (Videos 83.2 and 83.3). With advance warning, a normal person can recover within two steps. The examiner should always be prepared to catch the patient when this test is conducted; otherwise, a person who has lost postural reflexes could fall. The examiner should have a solid wall behind him or her in case a heavy patient falling backward also causes the examiner to fall backward. As postural reflexes are impaired, the patient collapses into the chair on attempting to sit down (sitting

en bloc). Walking can be marked by festination, whereby the patient walks faster and faster, trying to move the feet forward to be under the flexed body's center of gravity and thus prevent falling.

The *freezing* phenomenon (motor block) is a transient inability to perform active movements. It most often affects the legs when walking but also can involve eyelid opening (known as *apraxia of lid opening* or levator inhibition), speaking (*palilalia*), and writing. Freezing occurs suddenly and is transient, lasting usually no more than several seconds with each occurrence. The feet seem as if "glued to the ground" and then suddenly become "unstuck," allowing the patient to walk again (Video 83.3). Freezing typically occurs when the patient begins to walk (start hesitation); turns while walking; or approaches a destination, such as a chair in which to sit (destination hesitation); it is often induced when the patient walks in crowded places (e.g., in the narrow confines of a theater row or when trying to go through a revolving door, or when suddenly confronted by a person coming into their path) and when there is a time restriction to the walking (e.g., trying to enter or exit an elevator before the door closes or when trying to cross a street before the traffic light turns to red). Freezing is often overcome by visual clues, such as having the patient step over objects, and is much less frequent when the patient is going up or down steps than when walking on level ground. The combination of freezing of gait and loss of postural reflexes is particularly devastating because it often leads to falls. Falling is responsible for the high incidence of hip fractures in parkinsonian patients.

SYMPTOMS AND SIGNS

The clinical signs and symptoms of PD can be divided into motor and nonmotor features of PD and those due to complications or adverse effects of the medications employed to treat the disease. The clinical motor features of PD are represented within the six cardinal features of parkinsonism discussed earlier. Of the six cardinal motor signs, tremor, bradykinesia, and rigidity occur early in the course of the disease, whereas flexed posture, loss of postural reflexes, and freezing of gait occur in more advanced stages. Falling is a late symptom. If these normally advanced signs and symptoms occur within 2 years of onset, one should suspect another cause of parkinsonism, such as progressive supranuclear palsy or MSA.

The onset of PD is insidious; tremor is the symptom first recognized in 70% of patients (Table 83.4). Symptoms often begin unilaterally; as the disease progresses, symptoms and signs become bilateral. The disease can remain confined to one side for several years before the other side becomes involved. The disease progresses slowly, and if untreated, the patient eventually becomes wheelchair-bound and bedridden. Despite having severe bradykinesia with marked immobility, patients, when presented with a sudden stimulus, may rise suddenly and move normally for a short burst of motor activity, so-called kinesia

paradoxica. The Hoehn-Yahr clinical staging (Table 83.5) captures the progression of the motor features of PD, from unilateral to bilateral, to loss of postural reflexes to disability. Disability in carrying out activities of daily living is scored on the Schwab-England scale. More detailed scoring of individual signs and symptoms of PD are captured in the Unified Parkinson's Disease Rating Scale (UPDRS) and its newer version that includes more nonmotor symptoms, the Movement Disorder Society (MDS)-UPDRS.

TABLE 83.4 Initial Symptoms in Parkinson Disease

Symptoms	No. of Cases ($n = 183$)	Percentage
Tremor	129	70.5
Stiffness or slowness of movement	36	19.7
Loss of dexterity and/or handwriting disturbance	23	12.6
Gait disturbance	21	11.5
Muscle pain, cramps, aching	15	8.2
Depression, nervousness, or other psychiatric disturbance	8	4.4
Speech disturbance	7	3.8
General fatigue, muscle weakness	5	2.7
Drooling	3	1.6
Loss of arm swing	3	1.6
Facial masking	3	1.6
Dysphagia	1	0.5

Paresthesia	1	0.5
Average number of initial symptoms per patient		**1.4**

TABLE 83.5 The Modified Hoehn and Yahr Staging Scale for Parkinson Disease

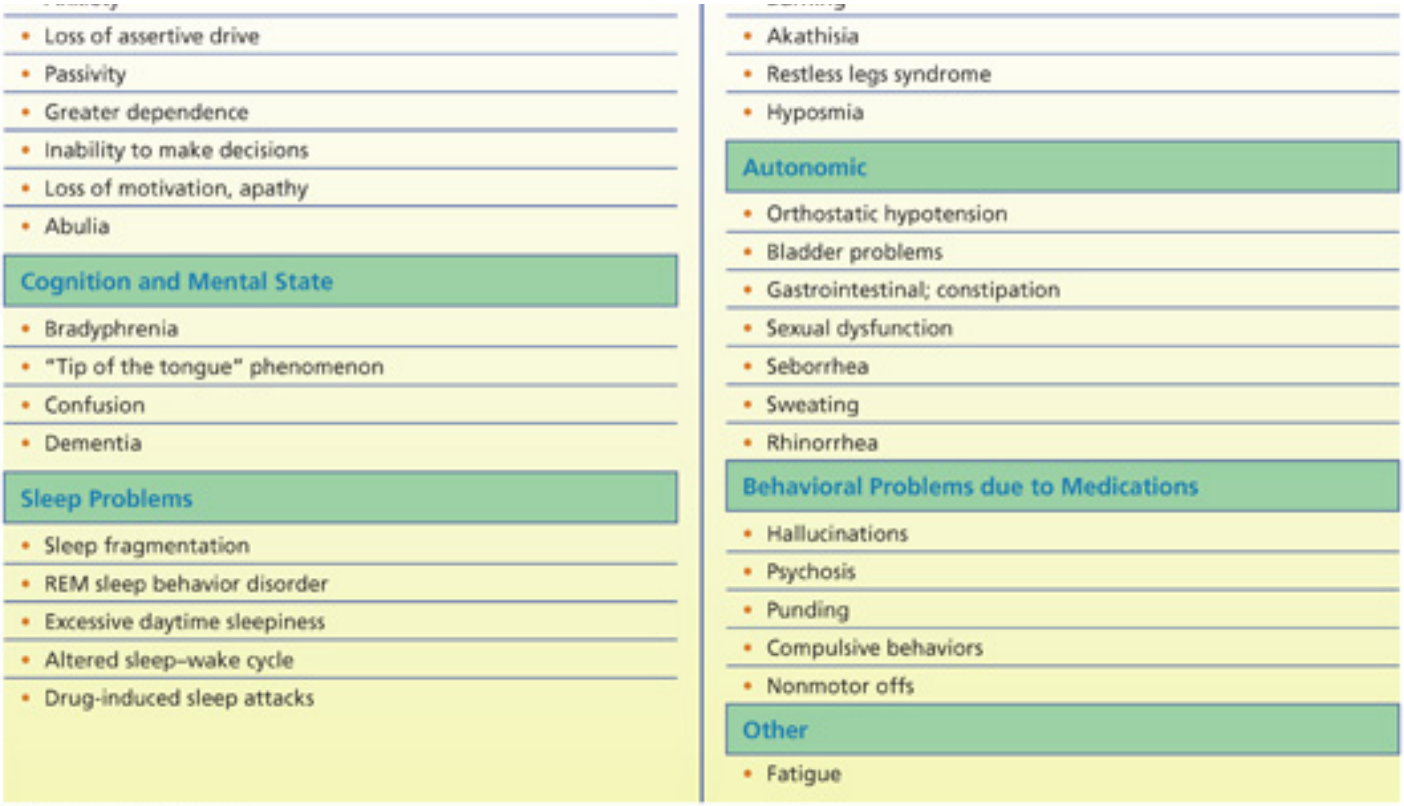
Stage 0	No signs of disease
Stage 1	Unilateral disease
Stage 1.5	Unilateral plus midline/axial involvement
Stage 2	Bilateral disease, without impairment of balance
Stage 2.5	Mild bilateral disease, with an abnormal pull test but with recovery to avoid falling
Stage 3	Mild to moderate bilateral disease; some postural instability (would fall on the pull test if not caught); physically independent
Stage 4	Severe disability; still able to walk or stand unassisted, but a walking aid is advisable to prevent falling
Stage 5	Wheelchair-bound or bedridden unless aided

From Fahn S, Elton RL, Members of the UPDRS Development Committee. The unified Parkinson's disease rating scale. In Fahn S, Marsden CD, Calne DB, et al, eds. *Recent Developments in Parkinson's Disease*. Vol. 2. Florham Park, NJ: Macmillan Healthcare Information; 1987:153–163, 293–304.

The nonmotor symptoms of PD (Table 83.6) can be more troublesome than the motor features of PD. Behavioral and personality changes include a reduced attention span, visuospatial impairment, and a personality that slowly becomes more dependent, fearful, indecisive, and passive. The spouse gradually makes more of the decisions and becomes the dominant partner. The patient speaks less spontaneously. The patient eventually sits much of the day and is inactive unless encouraged to exercise. Passivity and lack of motivation are common and are expressed by the patient's aversion to visiting friends. The patient is more reticent to participate in conversations. Depression is frequent in patients with PD, with about 25% to 50% prevalence. Anxiety may be even more common, often with depression.

TABLE 83.6 Nonmotor Features of Parkinson Disease

Personality and Behavior	Sensory
• Depression	• Pain
• Fearfulness	• Paresthesia, numbness
• Anxiety	• Burning



REM, rapid eye movement.

Cognitive decline is not an early feature but can become pronounced as the patient ages. Memory impairment, in contrast to AD, is not a feature of early PD; rather, the patient is just slow in responding to questions, so-called bradyphrenia. The correct answer can be obtained if the patient is given enough time. Subtle signs of bradyphrenia include tip-of-the-tongue phenomena from diminished verbal fluency and the inability to change mental set rapidly. In a cross section of patients with PD, 15% to 20% have a more profound dementia, but as many as 75% will develop dementia in their late 70s. Most of these patients have developed Lewy bodies in cortical neurons (Parkinson disease dementia [PDD]), and some have developed concurrent AD. These disorders are not always distinguishable, but dementia with Lewy bodies is often characterized by fluctuating hallucinations.

Sensory symptoms are fairly common, but objective sensory impairment is not seen in PD. Symptoms of pain, burning, and tingling occur in the region of motor involvement. A patient may have dull pain in one shoulder as an early symptom of the disease, which often is misdiagnosed as arthritis or bursitis, and even before clear-cut signs of bradykinesia appear in that same arm. Akathisia (inability to sit still, restlessness) and the restless legs syndrome (RLS) occur in some patients with PD. In both syndromes, uncomfortable sensations disappear with movement, and sometimes, the two conditions are difficult to distinguish. Akathisia, if present, is usually present most of the day; it may respond to levodopa but otherwise has not been treated successfully. The RLS develops late in the day with crawling sensations in the legs and may be associated with periodic movements in sleep, thereby disturbing sleep. Other sleep problems are fragmented sleep and rapid eye movement (REM) sleep behavior disorder (acting out one's dreams); the latter is usually successfully treated with clonazepam; melatonin may also provide relief. Other sleep problems are encountered with dopaminergic medications including excessive daytime sleepiness and sudden attacks of sleep without warning.

Autonomic disturbances also are encountered. The skin is cooler, constipation is a major complaint, bladder emptying is inadequate, erection may be difficult to achieve, and blood pressure may be low. Orthostatic hypotension is not uncommon and is made worse with dopaminergic medications. A major diagnostic consideration is the dysautonomia of MSA, which often has features of parkinsonism and cerebellar dysfunction. Seborrhea and seborrheic dermatitis are common but can be controlled with good hygiene and facial cleansing. Other nonmotor features of PD are reduced sense of smell (hyposmia), rhinorrhea, and excessive sweating.

Tendon reflexes are usually unimpaired in PD; an abnormal extensor plantar reflex suggests a Parkinson-plus syndrome, but an extension of the big toe "striatal toe" is seen in PD and can mimic a Babinski sign. More common is flexion of the toes on the involved side of the body; this can be the presenting complaint. An uninhibited glabellar reflex (Myerson sign) and palmomental reflexes are common, even early in the disease.

DIFFERENTIAL DIAGNOSIS

The diagnosis of PD is based on the clinical features of parkinsonism; insidious asymmetric onset; slow worsening of symptoms; and the lack of other findings in the history, examination, or laboratory tests that would point to some other cause of parkinsonism (see Tables 83.1 and 83.7). The presence of rest tremor and substantial benefit from levodopa strongly support the diagnosis of PD. One of the most common disorders mistaken for PD is ET (see Chapter 73), which is characterized by postural and kinetic tremor, and not rest tremor unless the disease is advanced. Some patients with ET eventually develop PD. MRI is normal in PD, unless dementia or some other disorder is

present. Dopamine transporter (DAT) single-photon emission computed tomography (SPECT) or positron emission tomography (PET) and 3,4-dihydroxy-6-18F-fluoro-L-phenylalanine (FDOPA) PET correlate with decreased dopaminergic nerve terminals in the striatum; the caudal putamen is affected first. DAT SPECT is available in United States and in most of the rest of the world. It can be used to distinguish the diagnosis of PD from ET; the DAT scan is normal in ET. ^{18}F-fluorodeoxyglucose (FDG)-PET reveals hypermetabolism in the lentiform nucleus and a progressive metabolic network pattern that correlates with disease worsening. A different metabolic network pattern is associated with declining cognition in PD and also in Parkinson-plus syndromes.

Several clinical clues suggest that a patient with parkinsonism has some form of the syndrome other than PD itself (Table 83.7). In general, PD often presents with symptoms on only one side of the body, whereas patients with symptomatic parkinsonism or Parkinson-plus syndromes almost always have symmetric symptoms and signs (notable exceptions are cortical–basal syndrome and parkinsonism resulting from a focal brain injury, such as head trauma). Similarly, a rest tremor usually indicates PD because it much less often seen in symptomatic parkinsonism or Parkinson-plus syndromes, except in drug-induced and MPTP-induced parkinsonism, which do include rest tremor. The patient who does not have unilateral onset or rest tremor, however, still can have PD that begins symmetrically and without tremor. Perhaps the most important diagnostic aid is the response to levodopa. Patients with PD almost always have a clear-cut, satisfactory response to this drug. If a patient never responds to levodopa, the diagnosis of some other form of parkinsonism is likely. A response to levodopa, however, does not confirm the diagnosis of PD because many cases of symptomatic parkinsonism (e.g., MPTP, postencephalitic, reserpine induced) and many forms of Parkinson-plus syndromes in their early stages (e.g., MSA) also respond to levodopa. Table 83.7 provides a list of some helpful clues. Chapter 84 provides clinical descriptions of other parkinsonian disorders.

TABLE 83.7 Clues Indicate the Likely Type of Parkinsonism

Clinical	Alternative Diagnoses
Never responded to levodopa	Other than PD
Predominantly unilateral	PD; HP–HA syndrome; CBS
Symmetric onset	PD; most forms of parkinsonism
Presence of rest tremor	PD; secondary parkinsonism
Lack of rest tremor	PD; Parkinson-plus syndromes
History of encephalitis	Postencephalitic parkinsonism
History of toxin exposure	Parkinsonism caused by the toxin
Taking neuroleptics	Drug-induced parkinsonism
Shuffling gait much greater than upper limb bradykinesia	Normal pressure hydrocephalus; vascular parkinsonism
Severe unilateral rigidity	CBS

Severe unilateral rigidity	CBS
Cortical sensory signs	CBD
Unilateral cortical myoclonus	CBD
Unilateral apraxia	CBD
Alien limb	CBD
Early dementia	Dementia with Lewy bodies; AD; frontotemporal dementia
Psychotic sensitivity to levodopa	Dementia with Lewy bodies; AD
Early loss of postural reflexes	Progressive supranuclear palsy
Early falling	Progressive supranuclear palsy
Impaired downgaze	Progressive supranuclear palsy
MRI: caudate atrophy	HD; neuroacanthocytosis
MRI: decreased T2 signal in striatum	Multiple system atrophy
MRI: midbrain atrophy	Progressive supranuclear palsy
"Apraxia" of eyelid opening	Progressive supranuclear palsy
Deep nasolabial folds	Progressive supranuclear palsy
Furrowed forehead and eyebrows (quizzical look)	Progressive supranuclear palsy
Excessive hesitation between words when speaking	Progressive supranuclear palsy; CBD
Nuchal dystonia	Progressive supranuclear palsy
Abducted arms when walking	Progressive supranuclear palsy
Square wave jerks	Progressive supranuclear palsy; multiple system atrophy; CBS
Pure freezing	Progressive supranuclear palsy
Meaningful orthostatic hypotension	Multiple system atrophy
Urinary or fecal incontinence	Multiple system atrophy
Cerebellar dysarthria and dysmetria	Multiple system atrophy, SCA2, SCA3, SCA17
Laryngeal stridor (vocal cord paresis)	Multiple system atrophy
Lower motor neuron findings	Multiple system atrophy; neuroacanthocytosis
Upper motor neuron findings	Multiple system atrophy
Early orofacial dyskinesia with levodopa	Multiple system atrophy
Laboratory	
Fresh blood smear: acanthocytes	Neuroacanthocytosis
Grossly elevated creatine kinase	Neuroacanthocytosis
MRI: many lacunes	Vascular parkinsonism
MRI: "eye of the tiger" in pallidum	Pantothenate kinase–associated neurodegeneration (PKAN)
MRI: huge ventricles	Normal pressure hydrocephalus
Abnormal autonomic function tests	Multiple system atrophy
Denervation on sphincter EMG	Multiple system atrophy

PD, Parkinson disease; HP-HA, hemiparkinsonism–hemiatrophy; CBS, cortical-basal syndrome; CBD, cortical-basal degeneration; AD, Alzheimer disease; MRI, magnetic resonance imaging; HD, Huntington disease; SCA, spinocerebellar atrophy; EMG, electromyography.

TREATMENT

At present, treatment is aimed at controlling motor and nonmotor symptoms of PD because no drug or surgical approach unequivocally prevents progression of the disease, although some clinical trials suggest that monoamine oxidase-B (MAO-B) inhibitors may slow clinical progression. Treatment is individualized because each patient has a unique set of symptoms; signs; response to medications; and a host of social, occupational, and emotional needs that must be considered. The goal is to keep the patient functioning independently as long as possible. Practical guides are the symptoms and degree of

functional impairment and the expected benefits and risks of therapeutic agents. Much of the therapeutic effort in advanced PD involves controlling the motor adverse effects of levodopa, namely, dyskinesias and wearing-off.

Although pharmacotherapy is the basis of treatment, physiotherapy and exercise are also important [**Level 1**].[1] It involves patients participating actively in their own care, promotes exercise, keeps muscles active, preserves mobility, and improves balance. This approach is especially beneficial as parkinsonism advances because many patients tend to remain sitting and inactive. Psychiatric assistance may be required to deal with depression and anxiety and the social and familial problems that may develop with this chronic disabling illness. Electroconvulsive therapy may have a role in patients with severe intractable depression.

USEFUL DRUGS AND SURGICAL PROCEDURES

Table 83.8 lists the drugs useful in parkinsonism according to mechanisms of action. It also lists some of the surgical approaches available. Selection of the most suitable drugs for the individual patient and deciding when to use them in the course of the disease are challenges for the treating clinician. Because PD is chronic and progressive, treatment is lifelong. Medications and their doses change with time as adverse effects and new symptoms are encountered. Tactical strategy is based on the severity of symptoms.

TABLE 83.8 Therapeutic Choices for Parkinson Disease

Medications
• Dopamine precursor: levodopa ± carbidopa, standard and extended release
• Dopamine agonists: bromocriptine, pramipexole, ropinirole, apomorphine, cabergoline, rotigotine
• Catechol-*O*-methyltransferase inhibitors: entacapone and tolcapone
• Dopamine releaser: amantadine
• Glutamate antagonist: amantadine
• Monoamine oxidase type B inhibitors: selegiline and rasagiline
• Anticholinergics: trihexyphenidyl, benztropine, ethopropazine, biperiden, cycrimine, procyclidine. Weaker anticholinergics: diphenhydramine, orphenadrine, amitriptyline
• Muscle relaxants: cyclobenzaprine, diazepam, baclofen
• Peripheral antidopaminergic for nausea and anorexia: domperidone
• Antidepressants: amitriptyline and other tricyclics, fluoxetine and other serotonin uptake inhibitors

- Antianxiety agents: benzodiazepines
- Antipsychotics: clozapine, quetiapine
- Cholinesterase inhibitors for dementia: rivastigmine, donepezil
- REM sleep behavior disorder: clonazepam, melatonin
- Hypnotics: zolpidem, mirtazapine, amitriptyline, trazodone
- Antisoporific (daytime drowsiness): modafinil (Provigil), methylphenidate
- Anti–restless legs: dopamine agonists, pregabalin, gabapentin, opioids (e.g., propoxyphene, tramadol, oxycodone)
- Antisialorrhea: glycopyrrolate, propantheline, trospium (Sanctura), and other non–CNS-penetrating anticholinergics; botulinum toxin injection into salivary glands
- Antihypotensives: midodrine (ProAmatine), fludrocortisone, droxidopa
- Anticonstipation: high-fiber diet, polyethylene glycol (MiraLAX), and other laxatives

Surgery

- Ablative surgery
  - Thalamotomy
  - Pallidotomy
- Deep brain stimulation
  - Thalamic stimulation
  - Pallidal stimulation
  - Subthalamic stimulation

In Table 83.8, *carbidopa* is listed as the peripheral dopa decarboxylase inhibitor, but in many countries, *benserazide* is also available. These agents potentiate the effects of levodopa, thus allowing about a fourfold reduction in dosage to obtain the same benefit. Moreover, by preventing the formation of peripheral dopamine, which can act at the area postrema (vomiting center), they block the development of anorexia, nausea, and vomiting. *Domperidone* is a dopamine receptor antagonist that does not enter the CNS; it is used to prevent nausea not only from levodopa but also from dopamine agonists. Domperidone is not available in the United States. Providing larger doses of carbidopa may also reduce gastrointestinal adverse effects.

Of the listed dopamine agonists, bromocriptine, pramipexole, ropinirole, rotigotine, and apomorphine are available in the United States; they are reviewed in a later section. Pergolide and cabergoline affect heart valve serotonin (5-hydroxytryptamine) 2B (5HT2B) receptors and can cause a fibrotic valvulopathy. Pergolide is no longer available in the United States. Because it is not absorbed through the intestinal tract and it is water-soluble, apomorphine is used as an injectable, rapidly acting dopaminergic drug to overcome “off”

states (rescue effect). Subcutaneous apomorphine infusions are available in Europe, as are lisuride and cabergoline. Catechol-*O*-methyltransferase (COMT) inhibitors extend the elimination half-life of levodopa. Entacapone has a very short half-life and is given with each dose of levodopa. Tolcapone is longer-acting but requires monitoring for hepatotoxicity.

Amantadine, *selegiline*, *rasagiline*, and the anticholinergics are reviewed in following sections. Because the anticholinergics can cause forgetfulness and even psychosis, they should be used cautiously in patients most susceptible (those older than 70 years). The antihistaminics, tricyclics, and cyclobenzaprine have milder anticholinergic properties that make them useful in PD, particularly in the older patient who should not take the stronger anticholinergics. A number of medications listed in Table 83.8 are used to treat the many nonmotor problems seen in PD; these are discussed in a later section. The surgical procedures are also covered separately.

Levodopa is uniformly accepted as the most effective drug available for symptomatic relief of many of the motor features of PD. If it were uniformly and persistently successful and also free of complications, new strategies for other treatment would not be needed. Unfortunately, 75% of patients have serious complications after 5 years of levodopa therapy (Table 83.9).

TABLE 83.9 Five Major Outcomes after More Than 5 Years of Levodopa Therapy ($n = 330$ Patients)[a]

Smooth good response	$n = 83$ (25%)
Troublesome fluctuations	$n = 142$ (43%)
Troublesome dyskinesias	$n = 67$ (19%)

Toxicity at therapeutic or subtherapeutic dosages	*n* = 14 (4%)
Total or substantial loss of efficacy	*n* = 27 (8%)

[a]Thirty-six patients had both troublesome fluctuations and troublesome dyskinesias.

From Fahn S. Adverse effects of levodopa. In: Olanow CW, Lieberman AN, eds. *The Scientific Basis for the Treatment of Parkinson's Disease*. Carnforth, England: Parthenon; 1992:89–112.

TREATMENT ACCORDING TO THE STAGE OF PARKINSON DISEASE

EARLY STAGE

Authorities generally agree that in the early stage of PD when symptoms are noticed but not troublesome, symptomatic treatment is not necessary. All symptomatic drugs can induce side effects, and if a patient is not troubled socially or occupationally by mild symptoms, drug therapy can be delayed until symptoms become more pronounced. If disease-modifying therapies become available, they should be started at the time of diagnosis.

Selegiline delays the need for levodopa therapy by an average of 9 months. Because this MAO-B inhibitor provides a mild symptomatic effect, it has not been possible to conclude that selegiline also exerts a neuroprotective effect. However, a controlled study evaluating selegiline in the presence of levodopa therapy showed that those on selegiline performed better than subjects receiving placebo, including less development of the freezing phenomenon, thus, selegiline should be considered as a therapeutic option at the time the diagnosis of PD is made [**Level 1**].[2,3] Selegiline (dose: 5 mg with breakfast and lunch) has

few adverse effects when given without levodopa, but when given concurrently with levodopa, it increases the dopaminergic effect, allows a lower dose of levodopa, and contributes to dopaminergic-induced dyskinesias and hallucinations. *Rasagiline*, another irreversible propargylamine MAO-B inhibitor, also provides mild symptomatic effect, and controlled studies suggest it might have some disease-modifying effect as well (dose: 1 mg per day) [**Level 1**].[4] Exenatide showed promise of slowing progression in a pilot trial [**Level 1**].[5]

STAGE WHEN SYMPTOMS AND SIGNS REQUIRE SYMPTOMATIC TREATMENT

Eventually, PD progresses and symptomatic treatment must be used. The most common problems that clinicians consider important in deciding to use symptomatic agents are the following: threat to employment; threat to ability to handle domestic, financial, or social affairs; threat to handle activities of daily living; and appreciable worsening of gait or balance. In clinical practice, a global judgment for initiating such therapy is made in discussions between the patient and the treating physician.

The major decision is when to introduce levodopa, the most effective drug. All patients are likely to develop complications associated with long-term use (see Table 83.9). Younger patients, in particular, are more likely to show response fluctuations and dyskinesias, so other antiparkinsonian drugs, including dopamine agonists, could be used first to delay the introduction of levodopa in patients younger than age 50 years. This approach is known as the *levodopa-sparing strategy*. When symptoms threaten quality of life, levodopa is needed and should be administered at the lowest effective dose. High doses are more likely to induce the motor complications of dyskinesias and wearing-off. Concern that levodopa may hasten nigral dopaminergic neuronal degeneration has been largely diminished because a controlled trial, the ELLDOPA (earlier vs. later levodopa therapy in PD) study, showed that those with levodopa treatment actually are less impaired even after stopping medication for a few weeks (Fig. 83.2). The mechanism for this long-lasting improvement is not known.

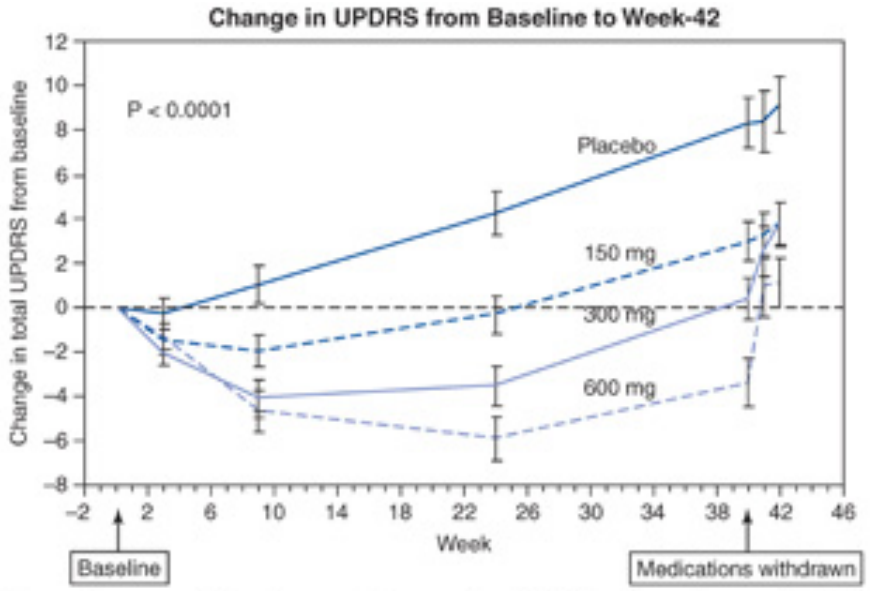


FIGURE 83.2 Effect of different dosages of levodopa on the severity of PD based on changes in the Unified Parkinson's Disease Rating Scale (UPDRS). Data are from the ELLDOPA study in which subjects with early, untreated PD were randomized equally to one of three doses of levodopa (with carbidopa) or placebo. Treatment lasted 40 weeks, after which the medication was tapered to zero over 3 days, and the subjects were evaluated 7 and 14 days later. The changes in subjects treated with levodopa at different dosages or with placebo were determined on the basis of the total score of UPDRS. The scores were obtained by the blinded treating investigator who performed the evaluations before the morning dose of the daily dose of the study drug. The points on the curves represent mean changes from baseline in the total scores at each visit. Improvement in parkinsonism is represented by lower scores and worsening by higher scores. Negative scores on the curves indicate improvement from baseline. The bars indicate standard error. The last 2 weeks (weeks 40 to 42) allowed a return of symptoms and signs, but those on levodopa did not reach the same degree of worsening seen in those treated with placebo. (Data from Parkinson Study Group. Levodopa and the progression of Parkinson's disease. *N Engl J Med.* 2004;351[24]:2498–2508.)

The drugs used in the levodopa-sparing strategy are discussed first, for these are tolerated in younger patients, who are most prone to develop motor complications from levodopa and who can often respond to these other drugs. For patients older than 70 years or those who have some cognitive impairment, levodopa is the preferred drug because it is the most effective with the least risk of inducing psychiatric adverse effects.

Amantadine

Amantadine is a mild indirect dopaminergic agent that acts by augmenting dopamine release at storage sites and possibly blocking reuptake of dopamine into the presynaptic terminals. It also has some anticholinergic and antiglutamatergic properties. In the early stages of PD, it is effective in about two-thirds of patients. A major advantage is that benefit, if it occurs, is seen in a couple of days. The effect can be substantial. Unfortunately, its benefit in more advanced PD is often short-lived, with patients reporting a fall-off effect after several months of treatment. A common adverse effect is livedo reticularis (a reddish mottling of skin) around the knees (these are not harmful); other adverse effects are ankle edema and visual hallucinosis. Sometimes, when the drug is discontinued, a gradual worsening of parkinsonian signs may follow, thus indicating that the drug has been helpful. The usual dose is 100 mg two times per day, but sometimes, a higher dose (up to 200 mg two times per day) may be required. Amantadine can be useful not only in the early phases of symptomatic therapy by forestalling use of levodopa or reducing the required dosage of levodopa but also in the advanced stages as an adjunctive drug to levodopa and the dopamine agonists. It can also reduce the severity of levodopa-induced dyskinesias, probably by its antiglutamatergic mechanism of action, and it is the most effective antidyskinetic drug available.

Anticholinergic (Antimuscarinic) Drugs

As a general rule, anticholinergic agents are less effective antiparkinsonian agents than are the dopamine agonists but may be more effective against tremor. The anticholinergic drugs are estimated to improve parkinsonism by about 20%. Many clinicians find that when tremor is not relieved by an agonist or levodopa, addition of an anticholinergic drug may be helpful. Trihexyphenidyl is a widely used anticholinergic agent. A common starting dose is 2 mg three times per day. It can be gradually increased to 15 mg or more per day.

Adverse effects from anticholinergic drugs are common, particularly in the age range of most patients with PD. Adverse cerebral effects are predominantly forgetfulness and decreased short-term memory. Occasionally, hallucinations and psychosis occur, particularly in the elderly patient; these drugs should be avoided in patients older than 70 years. If tremor is not relieved by dopaminergic drugs and one wishes to add an anticholinergic agent to the therapy for an elderly patient, amitriptyline, diphenhydramine, orphenadrine, or cyclobenzaprine is sometimes beneficial, with less CNS side effects of more potent agents. Diphenhydramine and amitriptyline can cause drowsiness and can be used as a hypnotic. For tremor control, the dose is increased gradually to 50 mg three times per day. A similar dose schedule is useful for orphenadrine. Cyclobenzaprine can be increased gradually until 20 mg three times per day is reached. Anticholinergics can reduce sialorrhea.

Peripheral side effects are common and are often the reason for discontinuing or limiting the dosage of anticholinergic drugs. Another approach is to treat peripheral adverse effects by appropriate antidotes. Pilocarpine eye drops can overcome dilated pupils that can cause blurred vision and can be useful if glaucoma is present. Pyridostigmine, up to 60 mg three times per day, can help to overcome dry mouth, urinary difficulties, and constipation.

Dopamine Agonists

Controlled trials comparing dopamine agonists and levodopa have been carried out [**Level 1**].[6,7] Dopamine agonists can be used as monotherapy in the early stage of the disease to delay introduction of levodopa or as conjunctive therapy with levodopa to potentiate an antiparkinsonian effect, to reduce the dosage needed for levodopa alone, and to overcome some of the adverse effects of long-term use of levodopa. Early use of dopamine agonists, by delaying the introduction of levodopa, delays the time to develop complications from chronic levodopa therapy such as motor fluctuations and dyskinesia. However, levodopa is added eventually for most patients on dopamine agonists and long-term follow-up studies show similar eventual prevalence of these complications in both groups [**Level 1**].[8]

The agonists are less effective than levodopa as antiparkinsonian agents, and most patients require the addition of levodopa within a couple of years. Bromocriptine, pergolide, lisuride, and cabergoline are ergot derivatives. As such, they could induce red inflamed skin (St. Anthony's fire), but this side effect is rare and is reversible on discontinuing the drug. Retroperitoneal, pleural, and pericardial fibrosis are more serious adverse, but also rare, events. Restrictive fibrotic cardiac valvulopathy may occur in up to one-third of patients taking pergolide (detected by echocardiography), due to its agonist effect on the heart valve 5HT2B receptors, and this drug is no longer available in the United States. The nonergoline agonists, pramipexole and ropinirole, are the most commonly used dopamine agonists. They can cause excessive daytime sleepiness and ankle edema (with redness of the skin). Sleep attacks, including falling asleep without warning when driving a vehicle, are infrequent problems with dopamine agonists, but drivers need to be cautioned about such a serious possibility. Observing sleep attacks at home when just sitting in a chair is a warning sign not to drive. Defensive methods, such as delaying a dose of agonist or taking a stimulant such as modafinil or methylphenidate before a long drive, may be reasonable, but studies on whether these approaches are effective have not been carried out. Besides sleep effects and ankle edema, dopamine agonists are more prone than levodopa to induce hallucinations, particularly in the elderly who already may have some cognitive impairment.

A serious behavioral adverse effect from dopamine agonists is the development of impulse control problems in approximately 17% of subjects. These consist of pathologic

gambling, hypersexuality, impulsive binge eating with weight gain, compulsive shopping, and excessive generosity, such as charitable contributions. Patients and their care providers need to be warned about this potential risk and the dosage markedly reduced or discontinued at the first sign of such a complication. Fortunately, the impulse control problem is reversible but usually requires discontinuation of these agents. Rapid elimination can induce a withdrawal reaction, so a gradual taper of the drug is preferred.

All agonists can induce anorexia and nausea. Orthostatic hypotension tends to occur when the drug is first introduced. Afterward, this complication is much less common. Therefore, the best starting regimen is a small dose at bedtime for the first 3 days (bromocriptine 1.25 mg, pramipexole 0.125 mg, ropinirole 0.25 mg) and then a switch from bedtime to daytime regimens at this dose for the next few days. The daily dose can be increased gradually at weekly intervals to avoid adverse effects (bromocriptine 1.25 mg, pramipexole 0.25 mg, ropinirole 0.75 mg) until a benefit or a plateau dosage is reached (bromocriptine 5 mg three times per day, pramipexole 0.5 mg three times per day, ropinirole 1 mg three times per day). If this plateau is not satisfactory, the dose either can be increased gradually until it is quadrupled or can be held constant while beginning carbidopa/levodopa. Extended-release tablets of pramipexole and ropinirole are also available and can be given once a day. The same total daily dose as the immediate release formulations provides similar effects.

Rotigotine is not absorbed via the intestinal tract but is absorbed transdermally. It is available as a dermal patch, with absorption over 24 hours. It is a weak dopamine agonist, but the once-a-day dermal patch application is convenient, and as such allows day-long plasma levels of the agonist, which theoretically could reduce wearing-off and nocturnal akinesia.

Besides the adverse effects listed earlier, there are subtle differences among the dopamine agonists. Cabergoline has the longest pharmacologic half-life and theoretically could be taken in once-a-day dosing, but valvulopathy is a risk. All agonists act at the D2 receptor, which may account for most, if not all, of their anti-PD activity (Table 83.10). Pergolide acts at both the D1 and D2 dopamine receptors. Bromocriptine is a partial D1 antagonist. Pergolide, pramipexole, and ropinirole also act at the D3 dopamine receptor, but it is not clear what effect this has clinically, but it is conceivable that the D2/D3 ratio may be instrumental in causing the impulse control problems seen with these drugs. All three appear to be equally effective against PD; bromocriptine appears to have the weakest anti-PD effect. Dopamine agonists, when used in the absence of levodopa, rarely induce dyskinesias. Whether this is because of their longer half-life and possibly more continuous dopaminergic receptor stimulation or because they exert a different receptor effect than that of levodopa is unknown. If the agonists alone are not sufficiently effective, carbidopa/levodopa is needed.

TABLE 83.10 Effect on Receptors by Dopamine Agonists

Agonist	D1	D2	D3	D4	D5	5-HT Receptor
Bromocriptine	−	+	++	+	+	0
Pergolide	+	++	+++	?	+	++
Pramipexole	−	++	++++	++	?	?
Ropinirole	−	++	++++	+	−	?
Cabergoline	−	+++	?	?	?	++
Lisuride	+	++	?	?	?	+

+, activates; −, inhibits; 0, no effect; ?, uncertain.

Levodopa

In controlled trials comparing levodopa and agonists as initial therapy, levodopa produced a superior clinical response but more fluctuations and dyskinesias as noted earlier. Some clinicians prefer to begin therapy with carbidopa/levodopa for early symptomatic treatment and to add an agonist after a small dose has been reached (e.g., 25/100 mg three times per day). This approach is particularly useful if a patient already has some disability. The advantage of using levodopa at this stage in preference to a dopamine agonist is that a therapeutic response is virtually guaranteed. Nearly all patients with PD respond to levodopa and do so quickly. In contrast, only some benefit derives adequately from a dopamine agonist alone, and it may take months to discover this because of a slower buildup of dosage. Therefore, if a definite response is needed quickly (e.g., to remain at work or to be self-sufficient), levodopa is preferable. On the other hand, if there is no particular urgency for a rapid clinical response and if the patient has no cognitive problems and is younger than 50 years of age, then beginning with a dopamine agonist allows one to use the levodopa-sparing strategy. Patients older than 70 years are less likely to develop response fluctuations with levodopa and more likely to develop confusion and hallucinations with dopamine agonists, so in this population, carbidopa/levodopa would be a good choice as a starting drug.

STAGE WHEN SYMPTOMS AND SIGNS REQUIRE TREATMENT WITH LEVODOPA

When other antiparkinsonian medications are no longer bringing about a satisfactory response, levodopa is required to reduce the severity of parkinsonism. Levodopa is the most potent anti-PD drug. In treating patients with PD, the rule of thumb has been to use the lowest dosage that can bring about adequate symptom reversal, not the highest dosage that the patient can tolerate. As previously mentioned, the longer the duration of disease and the higher the dose, the greater the likelihood motor complications will occur. After 5 years of levodopa therapy, about 75% of patients with PD have some form of troublesome complication (see Table 83.9). On the other hand, a dose-response study showed a clear-cut dose-related clinical benefit, which is an advantage with higher dosages (see Fig. 83.2) [**Level 1**].[9]

Combining levodopa with a peripheral dopa decarboxylase inhibitor (e.g., carbidopa) increases therapeutic potency and reduces gastrointestinal adverse effects, which can also be mitigated by increasing the dosage of levodopa slowly. A safe approach is to start with

half tablet of 25/100 mg strength carbidopa/levodopa once a day. Continue for a week and weekly increase by another half tablet. By the sixth week, a plateau dose of 25/100 mg three times daily is reached. Giving levodopa with meals during this titration phase will reduce the risk for anorexia and nausea. If there is inadequate benefit, continue to increase the dose but at a faster rate. The 25/250-mg tablets can also be used, and a dose of 25/250 mg three or four times a day is common in patients with more advanced disease.

Extended-release forms of carbidopa/levodopa (Sinemet CR) and benserazide/levodopa (Madopar HBS) provide a longer half-life and a lower peak plasma level of levodopa. In the early stage of levodopa therapy, when complications have not yet developed, use of extended-release carbidopa/levodopa had not proven advantageous over the use of the standard preparation in a controlled trial because it did not delay motor fluctuations. However, it may be useful to start treatment with such an extended-release preparation in elderly patients to avoid too high a brain concentration of levodopa that might induce side effects such as drowsiness.

Once response fluctuations have developed, the extended-release preparation could reduce mild wearing-off. Also, a bedtime dose often allows more mobility during the night. Disadvantages are a delay in the response with each dose, less reliability of absorption, and the possibility of a late-in-the-day excessive dyskinesia response that can be prolonged. For a quick response on awakening, patients often take the standard (immediate release) preparation as the first morning dose in addition to the extended-release form. Some patients need a combination of standard and extended-release preparations of levodopa throughout the day to obtain a smoother response and minimize their motor complications.

The extended-release tablets of carbidopa/levodopa are available in two strengths: scored (50/200 mg, which can be broken in half) and unscored (25/100 mg). Neither should be crushed because the matrix of the tablet that delays solubilization would no longer be intact. When added to a dopamine agonist, a dose of 25/100 mg three to four times per day often suffices. When used alone, a starting dose of 25/100 mg three times per day often is necessary and can be increased as needed to 50/200 mg three or four times per day. For those desiring to produce a continuous dopaminergic stimulation effect, multiple dosing a day should be considered. If greater relief is required, a dopamine agonist or standard carbidopa/levodopa should be added.

It should be noted that the entire content of the extended-release formulation is not absorbed before the tablet passes through the duodenum and jejunum (the sites where levodopa is absorbed), so that an equivalent dose needs to be approximately 1.3 times greater than a dose of standard carbidopa/levodopa to achieve the same clinical efficacy. A combination of immediate and extended release carbidopa/levodopa in capsules (Rytary) has become available; it has a longer half-life and may offer advantages in some patients.

Some clinicians attempt to extend the plasma half-life of levodopa by adding a COMT inhibitor, such as entacapone, with each dose of levodopa. A clinical trial found such a combination resulted in earlier dyskinesias than levodopa alone.

INADEQUATE RESPONSE TO LEVODOPA TREATMENT

As a general rule, the single most important piece of information to help the differential diagnosis of PD and other forms of parkinsonism is the response to levodopa. If the response is nil or minor, the disorder probably is not PD. An adequate response, however, does not ensure the diagnosis of PD. All presynaptic disorders (e.g., reserpine-induced, MPTP-induced, postencephalitic parkinsonism) respond to levodopa. Also, a response to levodopa can occur in the early stages of MSA and progressive supranuclear palsy; only later, when striatal dopamine receptors are lost, is the response lost.

Before concluding that levodopa is without effect in a given patient, an adequate dose must be tested. Not every symptom has to respond, but bradykinesia and rigidity respond best, whereas tremor can be resistant. Therefore, if rest tremor is the only symptom, lack of improvement does not exclude the diagnosis of PD. Tremor may never respond satisfactorily, even if adjunctive antiparkinsonian drugs are also used. Before concluding that *carbidopa/levodopa* is ineffective, a dose up to 2,000 mg levodopa per day should be tried if tolerated. If anorexia, nausea, or vomiting prevent attainment of a therapeutic dosage, the addition of extra carbidopa (additional 25 mg four times per day) or domperidone (10 to 20 mg before each levodopa dose) is usually effective in overcoming the adverse effect. If other adverse effects (drug-induced dystonia, psychosis, confusion, sleepiness, postural hypotension) prevent attainment of an effective dose, uncertainty about the diagnosis of PD will continue. In particular, dystonia induced by low doses of levodopa suggests a diagnosis of MSA. Similarly, drug-induced psychosis suggests PDD, diffuse Lewy body disease, or accompanying AD. Clozapine or quetiapine may suppress psychosis and allow the use of levodopa.

COMPLICATIONS OF LONG-TERM LEVODOPA THERAPY

Response fluctuations (wearing-off), dyskinesias, and behavioral effects are the major problems encountered with long-term levodopa therapy (Tables 83.11 and 83.12). These problems are features of an advanced stage of PD.

TABLE 83.11 Major Fluctuations and Dyskinesias as Complications of Levodopa

Fluctuations (Offs)	Dyskinesias
• Slow "wearing-off"	• Peak-dose chorea and dystonia
• Sudden "off"	• Diphasic chorea and dystonia
• Random "off"	• "Off" dystonia
• Yo-yoing	• Myoclonus
• Episodic failure to respond (dose failures)	
• Delayed "on"	
• Weak response at end of day	
• Varied response in relationship to meals	
• Sudden transient freezing	

TABLE 83.12 Behavioral Adverse Effects with Levodopa

- Drowsiness
- Delusions
- Reverse sleep–wake cycle
- Paranoia
- Vivid dreams
- Confusion
- Benign hallucinations
- Dementia
- Malignant hallucinations
- Behavioral "offs"
  - Depression, anxiety, panic, pain, akathisia, dysphoria

FLUCTUATIONS

Response to dopaminergic drugs consists of the short-duration response (SDR) within the time frame of hours and the long-duration response (LDR) that develops more slowly over weeks or longer. When levodopa therapy is initiated, the benefit from levodopa is usually sustained, with general improvement throughout the day and no dose-timing variations; mostly consisting of LDR. Skipping a dose is usually without loss of effect, and the response is evident on arising in the morning despite the lack of medication throughout the night. The pharmacokinetics of levodopa show a short initial distribution phase with a half-life of 5 to 10 minutes, a peak plasma concentration in about 30 minutes, and an elimination phase of about 90 minutes. Brain levels follow plasma levels. The mechanism for the LDR of levodopa is not known. It cannot be explained by a prolonged storage of dopamine from exogenous levodopa in residual nigrostriatal nerve terminals, and basal ganglia circuitry plasticity is probably responsible for this phenomenon.

With chronic levodopa therapy, however, most patients, including all patients with onset before age 40 years, begin to experience fluctuations. At first, fluctuations take the form of wearing-off (also known as *end-of-dose deterioration*), which is defined as a return of parkinsonian symptoms in less than 4 hours after the last dose. Gradually, the duration of benefit shortens further and the "off" state becomes more profound. The magnitude of the SDR to levodopa in patients with fluctuations may increase because the loss of the LDR leads to worse "off" states and patients notice fluctuations more readily due to greater difference between "on" and "off" states.

In some patients, these fluctuations become more abrupt in onset and random in timing; the condition is then the "on–off" effect and cannot be related to the timing of the levodopa intake. Motor "offs" are often accompanied by changes in mood (depression, dysphoria), anxiety, thought (more bradyphrenia), sensory symptoms (pain, akathisia), and dysautonomia (excessive sweating, urgency). Such behavioral, sensory, and autonomic "offs" can occur in the absence of motor "offs" and then they are difficult to recognize. Patients, in order to eliminate these unpleasant sensations, often take more frequent doses of levodopa, which has led some clinicians to call this the *dopamine disequilibrium syndrome*.

The brief peripheral half-life of levodopa, by itself, is not likely to be responsible for fluctuations. The half-life, present from the beginning of treatment, does not change. Also, no difference exists in the pharmacokinetics in patients with early disease who show a stable response and in those with advanced disease and fluctuations. Loss of striatal storage sites of dopamine by itself is not the sole cause of fluctuations either. The central effects on basal circuitry are likely to be involved. Some hypothesize that intermittent (compared with continuous) administration of levodopa contributes to the development of motor complications. These peaks and valleys of brain dopamine levels are thought to alter

the striatal dopaminoceptive medium spiny GABAergic neurons and their synaptic connections with other striatal interneurons and cortical afferents that provide glutamatergic input.

Once established, motor complications are seemingly irreversible. Substituting dopamine agonists for levodopa therapy or maintaining plasma concentrations at a constant therapeutic level by chronic infusion of levodopa diminishes the severity of the complications but does not eliminate them. Jejunal infusions of levodopa via a catheter inserted via the abdominal wall into the stomach and then passed into the jejunum, subcutaneous infusions of apomorphine, and hourly oral administration of liquefied levodopa have been used to "smooth out" the effect of levodopa. Selegiline, rasagiline, and COMT inhibitors are partially effective in treating mild wearing-off problems, probably by prolonging dopamine levels at the synapse [**Level 1**].[10] The addition of these drugs to patients taking levodopa, however, may lead to dopaminergic side effects, including increased dyskinesias, confusion, and hallucinations. Another approach is to combine the slow-release forms of carbidopa/levodopa (Sinemet CR) with the standard (immediate-release) form. Again, this approach is effective mainly on wearing-off problems and not on complicated on–off fluctuations. Furthermore, the sustained-release formulation results in less predictable plasma levels of levodopa and often increases dyskinesias. Standard carbidopa/levodopa can be given alone by shortening the interval between doses. For the more severe state of on–off phenomenon, a more rapid and more predictable response sometimes can be achieved by dissolving the levodopa tablet in carbonated water or ascorbic acid solution because an acidic solvent can both dissolve levodopa and prevent its auto-oxidation. Liquid levodopa enters the small intestine faster, is absorbed faster, and can be used to fine-tune dosing. Patients with fluctuations often develop delayed "ons" and dose failures resulting from delayed entry of levodopa into the small intestine. Liquefying or crushing levodopa by the patient's teeth can help resolve this problem.

A large meal that slows gastric emptying and high-protein meals can cause dose failures in some patients. Levodopa is absorbed from the small intestine by the transport system for large neutral amino acids and thus competes with these other amino acids for this transport. Patients with this problem may benefit by taking levodopa before meals and also from special diets that contain little protein for the first two meals of the day, followed by a high-protein meal at the end of the day when they can afford to be "off."

Direct-acting dopamine agonists, with their biologic half-lives longer than that of levodopa, can be used in combination with standard or slow-release forms of levodopa. The agonists are useful for treating both wearing-off and on–off by reducing both the frequency and the depth of the "off" states. In yet another approach to treating on–offs, the patients inject themselves with apomorphine subcutaneously to quickly return to the "on" state. Trimethobenzamide or the peripheral dopamine receptor antagonist domperidone can

be used to block nausea and vomiting from apomorphine.

DYSKINESIAS

Dyskinesias are commonly encountered with levodopa therapy but are often mild enough to be unnoticed by the patient. Severe forms, including chorea, ballism, dystonia, or combinations of these, can be disabling. The incidence and severity increase with duration and dosage of levodopa therapy, but they may appear early in patients with severe parkinsonism. Dyskinesias are divided into the following categories according to the timing of levodopa dosing:

1. Peak-dose dyskinesias appear at the height of antiparkinsonian benefit (20 minutes to 2 hours after a dose).
2. Diphasic dyskinesias, usually affecting the legs, appear at the beginning and end of the dosing cycle. Often, these may be mostly noticed by the patient at the end of the dose, blending into tremor that occurs during "off" state (see Video 83.4).
3. "Off" dystonia, which can be painful sustained cramps, appears during "off" states and may be seen at first as "early-morning dystonia" presenting as painful foot cramps; these are relieved by the next dose of levodopa.

Dyskinesias are usually seen in patients who have fluctuations, and some patients may move rapidly from severe peak-dose dyskinesias to severe "offs"; this process is known as *yo-yoing*. These patients may have only a brief "on" state. More commonly, they have good "ons" for parts of the day but are intermittently disabled by dyskinesias or "offs." These diurnal variations are major problems; patients with this combination have a narrow therapeutic window for levodopa. The mechanisms for dyskinesias, fluctuations, and good response that lead to "on" are not well understood, and they may have common pathways as well as differential ones. For example, those with dyskinesias are usually good responders to dopaminergic agents and many drugs that reduce dyskinesia may make parkinsonism worse. On the other hand, sensitivity to dyskinesias is not altered by chronic infusion of levodopa, whereas fluctuations are suppressed. Because dopamine agonists are much less likely to cause dyskinesias, which have much less activation of the D1 receptor, increased sensitivity and response of the D1 receptor by dopamine derived from levodopa are thought to play a role in the production of dyskinesias.

Amantadine can reduce the severity of dyskinesias, but a dosage of at least 400 mg/day is required, and it is not known how long the benefit may last. Treatment of peak-dose dyskinesias also includes reducing the size of each dose of levodopa. If doing so results in more wearing-off, the levodopa can be given more frequently with smaller dosages, or a dopamine agonist or inhibitor of MAO-B or COMT can be added with the reduced dose of levodopa. Diphasic dyskinesias are more difficult to treat. Increasing the dosage of

levodopa can eliminate this type of dyskinesia, but peak-dose dyskinesia usually ensues. A switch to a dopamine agonist as the major antiparkinsonian drug is more effective; low doses of levodopa are used as an adjunctive agent. The end-of-day dyskinesia is a part of the end-of-dose dyskinesia (part of diphasic dyskinesia). There is always a last dose of the day, and when that wears off, dyskinesias ensue. Medications such as amantadine and dopamine agonists rarely help end-of-day dyskinesias. Patients usually find that by taking the last dose of levodopa at home in the evening, and then allowing the dyskinesias to occur, lasting usually no more than 1 to 2 hours, the patient can live with this situation. Once the dyskinesia fades, the patient is then comfortable the rest of the evening. The principle of treating "off dystonia" is to try to keep the patient "on" most of the time. Here again, using a dopamine agonist as the major antiparkinsonian drug, with low doses of levodopa as an adjunct, can often be effective.

FREEZING

The freezing phenomenon is often listed as a type of fluctuation because of transient difficulty in initiating movement. But this phenomenon should be considered as distinct from the other types of fluctuations. "Off-freezing" must be distinguished from "on-freezing." Off-freezing, best considered a feature of parkinsonism itself, was encountered before levodopa was discovered. The treatment goal of off-freezing is to keep the patient from turning "off." On-freezing remains an enigma; it tends to be aggravated by increasing the dosage of levodopa or by adding direct-acting dopamine agonists or selegiline without reducing the dosage of levodopa. Rather, it may be lessened by reducing the dosage of levodopa. There is no satisfactory treatment for on-freezing. Both on- and off-freezing seem to correlate with both the duration of illness and the duration of levodopa therapy. Patients with a combination of complicated fluctuations, dyskinesias, and off-freezing may respond to subthalamic nucleus stimulation. On-freezing does not respond to surgical therapy.

MENTAL AND BEHAVIORAL COMPLICATIONS

The adverse effects of confusion, agitation, hallucinations, delusions, paranoia, and mania are probably related to activation of dopamine receptors in nonstriatal regions, particularly cortical and limbic structures. Both levodopa and dopamine agonists can cause these complications, with the latter more prone to do so. Elderly patients and those with diffuse Lewy body disease or concomitant AD are sensitive to small doses of these dopaminergics. But all patients with PD, regardless of age, can develop psychosis if they take excessive amounts of levodopa or agonists to overcome "off" periods. Patients with pronounced behavioral/sensory offs tend to take more and more levodopa.

Although antipsychotic drugs can reduce levodopa-induced psychosis, adding

neuroleptics that block D2 dopamine receptors worsens parkinsonism. Rather, quetiapine or clozapine, antipsychotic agents that preferentially block the dopamine D4 and serotonin receptors, can often treat psychosis without worsening parkinsonism. These drugs easily induce drowsiness, and they should be given at bedtime, starting with a dose of 12.5 mg. The dose can be gradually increased if necessary. Start with quetiapine to avoid the biweekly blood counts required with clozapine. Quetiapine is much less effective than clozapine, and it is not uncommon that clozapine is required. Because clozapine induces agranulocytosis in 1% to 2% of patients, patients must have blood counts monitored biweekly, and the drug must be discontinued if leukopenia develops. If clozapine is not tolerated, other drugs, including small doses of olanzapine, molindone, pimozide, or other relatively weak antipsychotic drugs, can be used. If the antipsychotic drugs increase the parkinsonism, lowering the dosage of levodopa to avoid the psychosis is preferable to maintaining the antipsychotic agent at high dosage. Levodopa cannot be discontinued suddenly because the abrupt cessation may induce a neuroleptic malignant-like syndrome.

Impulse control problems (gambling, hypersexuality, excessive eating, and shopping) induced by dopamine agonists or less commonly by levodopa can be devastating to the patient and family. Patients and families need to be aware about these potential problems so they can inform the treating physician. Fortunately, these problems are eliminated by reducing the dosage but sometimes only by discontinuing the agonists. Levodopa would need to substitute for the agonists.

Punding is a behavioral disorder that has a resemblance to the impulse control problems discussed earlier. The term was first used in amphetamine abusers and refers to an abnormal motor behavior in which there is intense repetitive handling and examining of objects, such as picking at oneself, taking apart watches and radios, or sorting and arranging of common objects, such as lining up pebbles, rocks, or other small objects. Punding has been reported with levodopa and dopamine agonists. Treatment is problematic, but atypical antipsychotics have been suggested.

TREATING THE NONMOTOR PROBLEMS OF PARKINSON DISEASE

Although many nonmotor symptoms can appear before the classic cardinal motor features of PD (e.g., hyposmia, REM sleep behavior disorder, depression, anxiety, constipation), many do not appear until later in the disease. Cognitive decline occurs late and is probably the most devastating nonmotor problem. When dementia occurs, the patient is not able to tolerate dopaminergics because of the susceptibility for psychosis, especially hallucinations, but also paranoia. Treatment of psychosis was discussed in the preceding section. Dementia is difficult to treat, but some response can be seen with the cholinesterase inhibitors, rivastigmine 1.5 to 6 mg twice a day and donepezil 5 to 10 mg/day. Antidepressants are needed for treating depression. The serotonin uptake

inhibitors are effective in treating depression of PD but may aggravate parkinsonism if antiparkinsonian drugs are not given concurrently. Tricyclics may be equally effective. Because of its anticholinergic and soporific effects, amitriptyline can be useful for these properties as well as for its antidepressant effect. Alprazolam, diazepam, and other benzodiazepines are usually well tolerated without worsening parkinsonism and can help to lessen tremor by reducing the reaction to stress that worsens tremor.

REM sleep behavior disorder, a condition where one moves while dreaming, is common in patients with PD. It is more troublesome for the bed partner than for the patient, but it can also cause the patient to fall out of bed and injure himself. It is extremely well treated with clonazepam at bedtime. Start with 0.5 mg and increase the dose if necessary. Sleep fragmentation is common in PD, and many patients have a difficult time falling back asleep after an arousal. A short-acting hypnotic given at that time (not at bedtime), such as zolpidem 5 mg, can provide relief. The other hypnotics listed in Table 83.8 can also be effective. If the patient requires an antipsychotic for vivid dreams, quetiapine or clozapine, which cause drowsiness, can be used instead of the hypnotics listed in the table. Excessive daytime sleepiness is another type of sleep problem that is common in PD; it is due to medications. Dopamine agonists commonly cause drowsiness, and in older patients with cognitive problems, levodopa can cause drowsiness at the peak of the dose. Modafinil up to 200 mg morning and midafternoon or methylphenidate up to 10 mg three times a day may provide some relief.

Many patients with PD develop RLS, which consists of unpleasant crawling sensations in the legs, particularly when sitting and relaxing in the evening, and which disappear on walking. Whether RLS is an epiphenomenon of PD, because both conditions respond to dopaminergics, is not clear. It is possible that RLS is a result of the dopaminergic medications used to treat PD. Sporadic and familial RLS respond to dopamine agonists and levodopa, but these drugs can cause augmentation, a worsening of the restless legs symptoms—more severe unpleasant sensations, occurring earlier in the day and spreading to involve other body parts. Fortunately, pregabalin 300 mg/day is effective [**Level 1**].[11] Opioids are also effective in treating RLS and periodic movements in sleep, whether in patients with PD or those with sporadic and familial RLS. Tramadol 25 mg late in the day before the onset of symptoms is usually effective, and one can titrate up to 150 mg/day if necessary. Oxycodone 5 to 15 mg, methadone 5 to 20 mg, and codeine 30 to 60 mg are also effective.

The varied autonomic symptoms in PD need to be treated specifically. Orthostatic hypotension can respond to midodrine, starting with 10 mg/day and titrate up to three doses a day if necessary. If midodrine is not effective, fludrocortisone can be used as well as adding salt to the diet. Combinations of these agents may be needed. Supine hypertension can be an adverse effect, and the head of the bed may need to be elevated to

avoid that. It is important that the patient's blood pressure, lying, sitting, and standing, be monitored by the family at home, reporting to the treating physician so the dosages of these agents can be properly adjusted. Droxidopa is a new agent approved for treating orthostatic hypotension. It is metabolized in the peripheral circulation to norepinephrine by the enzyme dopa decarboxylase. Thus, it will not be effective if more than 100 mg/day of carbidopa is being used.

Sialorrhea can be an annoying and embarrassing problem. Anticholinergics are effective, but most available agents are tertiary amines that enter the CNS and can impair memory or cause hallucinations in older patients. Quaternary amines, such as glycopyrrolate and propantheline, do not penetrate the CNS, and they are preferable. If such drugs are not completely effective, injections of botulinum toxin into the salivary glands can be attempted; an overdosage could impair swallowing, so an experienced physician should carry out the injections. Constipation is a common complaint. It should be treated with a high-fiber diet, supplemented by laxatives such as polyethylene glycol (MiraLAX).

SURGICAL THERAPY

Prior to the introduction of levodopa therapy, stereotactic surgery producing lesions in the thalamus or pallidum was common, resulting in reduction in tremor more than relief from other features of PD. Such surgery faded away after levodopa became available. But with the problems of motor complications from levodopa, there has been renewed interest in surgical therapy, mainly to treat these motor complications. The surgical approaches listed in Table 83.8 are not considered in the early stages of PD but are reserved for patients who respond to levodopa and who have developed intractable motor complications from it. Stereotaxic lesions have been largely replaced by high-frequency electrical stimulation at the same targets because of safety concerns. *Thalamotomy and thalamic stimulation* (the target for both is the ventral intermediate nucleus) are best for contralateral intractable tremor. Tremor can be relieved in at least 70% of cases. Although a unilateral lesion carries a small risk, bilateral operations result in dysarthria in 15% to 20% of patients. Thalamic stimulation seems to be safer and can be equally effective against tremor, but it runs the risks associated with foreign bodies and thin electronic wires that can break. *Pallidotomy and pallidal stimulation* (the target is the posterolateral part of the GPi) are most effective for treating contralateral dopa-induced dystonia and chorea but also have some benefit for bradykinesia and tremor. The target in the GPi is believed to be the site of afferent excitatory glutamatergic fibers coming from the subthalamic nucleus, which is overactive in PD.

Lesions of the subthalamic nucleus, although effective in relieving parkinsonism in animal models, are hazardous in humans because hemichorea or hemiballism may result.

Instead, *stimulation of the subthalamic nucleus* is used and appears to be the most effective in reducing contralateral bradykinesia and tremor [**Level 1**].[12] Indeed, the most common type of surgery today is to use electrical stimulation of the subthalamic nucleus. Such deep brain stimulation (DBS) provides a reduction in not only tremor but also bradykinesia and rigidity, allowing a reduction in dosage of dopaminergic medication. The antiparkinsonian effect is never better than the best levodopa effect (except for tremor in which surgery seems superior). It is not effective against symptoms that do not respond to levodopa (with the exception of intractable tremor, which can respond to stimulation). Therefore, DBS can be useful in patients with a very good anti-PD response to levodopa but with uncontrollable response fluctuations. DBS has the potential to smooth out these fluctuations. This type of surgery often allows a marked reduction in levodopa dosage, thereby reducing dopa-induced dyskinesias as well as treating parkinsonian symptoms. The best results are seen with younger patients. DBS in the GPi is superior for controlling dyskinesias. The presence of cognitive problems and lack of benefit from levodopa are contraindications. Cognitive problems worsen with surgical penetration in the brain. DBS produces levodopa-like benefits probably by restoring the physiologic balance in the basal ganglia circuitry, bypassing the need to restore dopamine levels. In this concept, DBS could be considered an "electronic levodopa." Adverse effects from the surgery include brain hemorrhage (rare), infection from a foreign body, speech impairment, dystonia, and breakage of the wires. Unfortunately, even in young patients, there can be impaired cognition, dysarthria, depression with suicide attempts, and incomplete control of fluctuations and dyskinesias. Targeting the GPi results in less dysarthria, depression, and cognitive impairment than the subthalamic nucleus. Experienced neurosurgeons and accurate placement of the electrodes are most important, and follow-up programming of the stimulators is an ongoing process to reach the ideal electrical settings. Exposure of the metallic stimulators to diathermy can result in permanent brain injury.

Pilot trials suggest that stimulation of the pedunculopontine nucleus can reduce falling, but results have been inconsistent. Controlled trials are needed to determine if falling and freezing of gait respond to the stimulation of this target. Controlled surgical trials of *fetal dopaminergic tissue implants* have found the benefits to be less efficacious than initially reported in open-label investigations and have also led to the development of persistent dyskinesias. Until this problem can be solved, transplantation surgery is not a useful option. The same concern exists for the potential of cellular therapy with dopaminergic stem cells. On the other hand, intrajejunal infusion of levodopa is already available and it offers a smooth pharmacokinetic profile of levodopa that reduces clinical fluctuations and dyskinesias [**Level 1**].[13] Percutaneous catheterization of the stomach with the catheter advanced into the jejunum avoids intracerebral penetration with its potential adverse effects.

OUTCOME

PD, being a neurodegenerative disease, worsens with time. Before the introduction of levodopa, PD caused severe disability or death in 25% of patients within 5 years of onset, in 65% in the next 5 years, and in 89% in those surviving 15 years. The mortality rate from PD was three times that of the general population matched for age, sex, and racial origin. Although no definite evidence indicates that levodopa alters the underlying pathologic process or stems the progressive nature of the disease, indications exist of a major impact on survival time and functional capacity. The mortality rate has dropped 50%, and longevity is extended by several years.

A debated point in the treatment of PD is the cause of declining efficacy from continuing treatment with levodopa seen in many patients. End-stage PD is denoted when the response to levodopa is inadequate to allow patient-assisted activities of daily living. Progression of the illness with further loss of dopamine storage sites in the presynaptic terminals cannot be the explanation for this outcome because loss of these structures in postencephalitic parkinsonism results in greater, not lower, sensitivity to levodopa. Perhaps as PD progresses, it is associated with loss of striatal dopamine receptors and loss of the presynaptic dopaminergic neuron.

After about 15 years of disease, most patients are seriously disabled, and the mortality rate increases compared to an age- and gender-matched population. Despite very effective medications for the early symptoms of PD, the motor symptoms of bradykinesia return and loss of postural reflexes constantly worsen, limiting ambulation. Falling and incurring fractures are common. In stage 5, patients require a wheelchair. Dysphagia with choking and aspiration and immobility with decubitus ulcers are common events. Dementia develops in most patients, rendering patients susceptible to psychosis with hallucinations and paranoid ideation. Patients become dependent on others for activities of daily living, and many are placed in nursing homes. Such a course emphasizes the importance of better understanding the pathogenesis and the need for disease-modifying therapy.

Videos can be found in the companion e-book edition. For a full list of video legends, please see the front matter.

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SUGGESTED READINGS

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