Chapter 435: Parkinson's Disease

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PARKINSON'S DISEASE AND RELATED DISORDERS

Parkinson's disease (PD) is the second most common age-related neurodegenerative disease, exceeded only by Alzheimer's disease (AD). Its cardinal clinical features were first described by the English physician James Parkinson in 1817. James Parkinson was a general physician who captured the essence of this condition based on a visual inspection of a mere handful of patients, several of whom he only observed walking on the street and did not formally examine. It is estimated that the number of people with PD in the most populous nations worldwide is ~5 million persons, and this number is expected to double within 20 years based on the aging of the population. The mean age of onset of PD is about 60 years, and the lifetime risk is ~3% for men and 2% for women. The frequency of PD increases with age, but cases can be seen in individuals in their twenties and even younger, particularly when associated with a gene mutation.

Clinically, PD is characterized by rest tremor, rigidity (stiffness), bradykinesia (slowing), and gait dysfunction with postural instability. These are known as the classical or "cardinal" features of the disease. Additional clinical features can include freezing of gait, speech difficulty, swallowing impairment, and a series of nonmotor features that include autonomic disturbances, sensory alterations, mood disorders, sleep dysfunction, cognitive impairment, and dementia **(see Table 435-1 and discussion below).**

TABLE 435-1

Clinical Features of Parkinson's Disease

CARDINAL MOTOR FEATURES	OTHER MOTOR FEATURES	NONMOTOR FEATURES
Bradykinesia	Micrographia	Anosmia
Rest tremor	Masked facies (hypomimia)	Sensory disturbances (e.g., pain)
Rigidity	Reduced eye blinking	Mood disorders (e.g., depression)
Postural instability	Drooling	Sleep disturbances (e.g., fragmented sleep, RBD)
	Soft voice (hypophonia)	Autonomic disturbances
	Dysphagia	Orthostatic hypotension
	Freezing	Gastrointestinal disturbances
	Falling	Genitourinal disturbances
		Sexual dysfunction
		Cognitive impairment/dementia

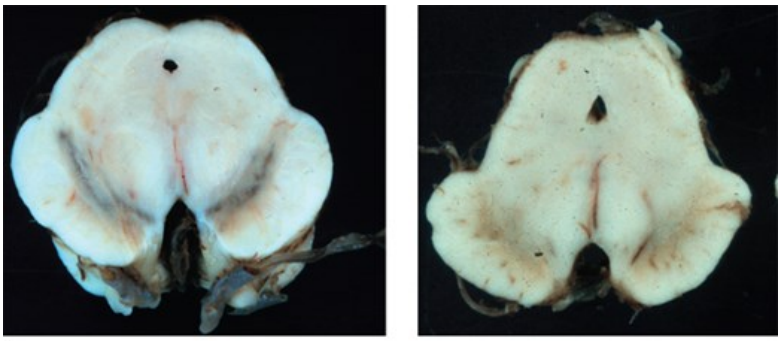
Abbreviation: RBD, rapid eye movement sleep behavior disorder.

Pathologically, the hallmark features of PD are degeneration of dopaminergic neurons in the substantia nigra pars compacta (SNc), reduced striatal dopamine, and intraneuronal proteinaceous inclusions in cell bodies and axons that stain for α-synuclein (known as Lewy bodies and Lewy neurites, collectively as Lewy pathology) **(Fig. 435-1)**. While interest has focused on the dopamine system, neuronal degeneration with Lewy pathology can also affect cholinergic neurons of the nucleus basalis of Meynert (NBM), norepinephrine neurons of the locus coeruleus (LC), serotonin neurons in the raphe nuclei of the brainstem, and neurons of the olfactory system, cerebral hemispheres, spinal cord, and peripheral autonomic nervous system. This "nondopaminergic" pathology is likely responsible for the nonmotor clinical features listed above and in Table 435-1. It has been postulated that Lewy pathology can begin in the peripheral autonomic nervous system, olfactory system, and dorsal motor nucleus of the vagus nerve in the lower

brainstem, and then spread in a predictable and sequential manner to affect the SNc and cerebral hemispheres (Braak staging). These studies thus suggest that the classic degeneration of SNc dopamine neurons and the cardinal motor features of PD develop at a midstage of the illness. Indeed, epidemiologic studies suggest that clinical symptoms reflecting early involvement of nondopaminergic neurons such as constipation, anosmia, rapid eye movement (REM) behavior sleep disorder, and cardiac denervation can precede the onset of the classic motor features of PD by several years if not decades. Originally it was considered that these are risk factors for developing PD, but based on pathological findings it is now considered likely that they represent an early premotor form of the disease. Intense efforts are underway to accurately define a premotor stage of PD with high sensitivity and specificity. This will be of particular importance when a neuroprotective therapy is available as it would be desirable to initiate disease-modifying treatment at the earliest possible stage of the disease.

FIGURE 435-1

Pathologic specimens from a patient with Parkinson's disease (PD) compared to a normal control demonstrating (***A***) reduction of pigment in SNc in PD (*right*) versus control (*left*), (***B***) reduced numbers of cells in SNc in PD (*right*) compared to control (*left*), and (***C***) Lewy bodies (*arrows*) within melanized dopamine neurons in PD. SNc, substantia nigra pars compacta.



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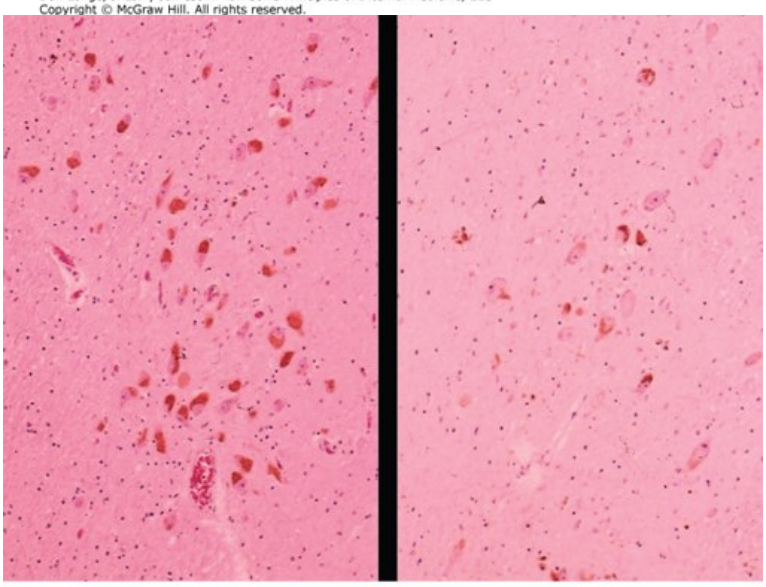

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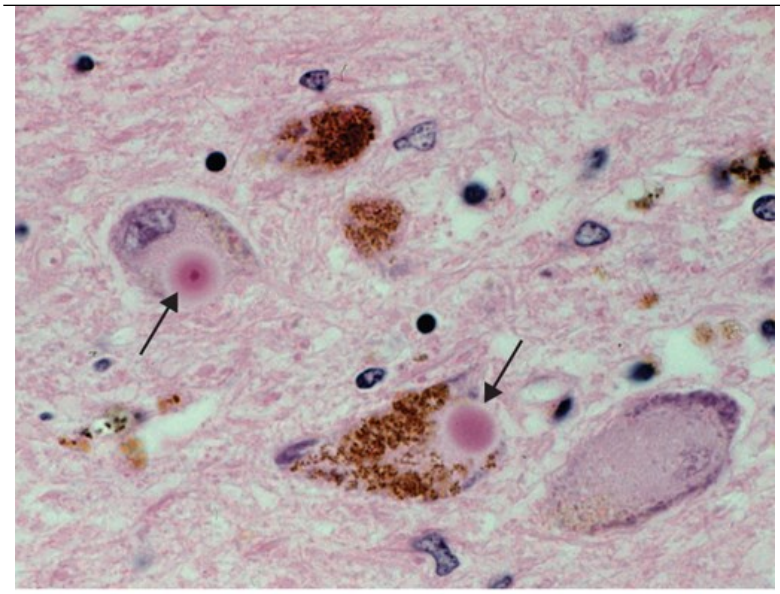


C

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

Parkinsonism is a generic term that is used to define a syndrome manifest by bradykinesia with rigidity and/or tremor. It has a differential diagnosis **(Table 435-2)** that reflects differences in the site of involvement within the basal ganglia, the nature of the pathology, and the clinical picture. The basal ganglia are comprised of a group of subcortical nuclei that include the striatum (putamen and caudate nucleus), subthalamic nucleus (STN), globus pallidus pars externa (GPe), globus pallidus pars interna (GPi), and the SNc **(Fig. 435-2)**. Among the different forms of parkinsonism, PD is the most common (~75% of cases). Historically, PD was diagnosed based on the presence of two of three parkinsonian features (tremor, rigidity, bradykinesia). However, postmortem studies found a 24% error rate when diagnosis was based solely on these criteria. Clinicopathologic correlation studies subsequently determined that parkinsonism (bradykinesia and rigidity) associated with rest tremor, asymmetry of motor impairment, and a good response to levodopa is much more likely to predict the correct pathologic diagnosis. With these revised criteria (known as the U.K. Brain Bank Criteria), a clinical diagnosis of PD could be confirmed pathologically in >90% of cases. Imaging of the dopamine system (see below) further increases diagnostic accuracy. The International Parkinson's Disease and Movement Disorder Society (MDS) has suggested revised clinical criteria for PD (known as the MDS Clinical Diagnostic Criteria for Parkinson's disease), which are thought to increase diagnostic accuracy even further, particularly in early cases where levodopa has not yet been tried. While motor parkinsonism has been retained as the core feature of the disease, the diagnosis of PD as the specific type of parkinsonism relies on three additional categories of diagnostic features: supportive criteria (features that increase confidence in the diagnosis of PD), absolute exclusion criteria, and red flags (which must be counterbalanced by supportive criteria to permit a diagnosis of PD). Utilizing these criteria, two levels of certainty have been delineated; clinically established PD and clinically probable PD (see Berg et al. Movement Disorders 30:1591, 2015 in Further Reading).

TABLE 435-2

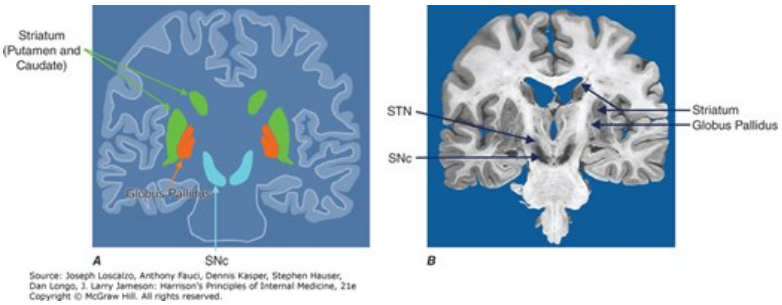
Differential Diagnosis of Parkinsonism

Parkinson's Disease Sporadic Genetic Dementia with Lewy bodies	Atypical Parkinsonism Multiple-system atrophy (MSA) Cerebellar type (MSA-c) Parkinson type (MSA-p) Progressive supranuclear palsy Parkinsonism variant Richardson variant Corticobasal syndrome Frontotemporal dementia	Secondary Parkinsonism Drug-induced Tumor Infection Vascular Normal-pressure hydrocephalus Trauma Liver failure Toxins (e.g., carbon monoxide, manganese, MPTP, cyanide, hexane, methanol, carbon disulfide)	Neurodegenerative disorders that are associated with parkinsonism Wilson's disease Huntington's disease Neurodegeneration with brain iron accumulation SCA 3 (spinocerebellar ataxia) Fragile X–associated ataxia-tremor-parkinsonism Prion diseases X-linked dystonia-parkinsonism Alzheimer's disease with parkinsonism Dopa-responsive dystonia

Abbreviation: MPTP, 1-methyl-4-phenyl-1,2,5,6-tetrahydropyridine.

FIGURE 435-2

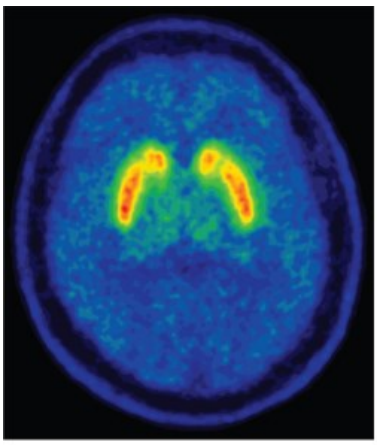
Basal ganglia nuclei. Schematic (***A***) and postmortem (***B***) coronal sections illustrating the various components of the basal ganglia. SNc, substantia nigra pars compacta; STN, subthalamic nucleus.



Imaging of the brain dopamine system in patients with PD can be performed using positron emission tomography (PET) or single-photon emission computed tomography (SPECT). These studies typically show reduced and asymmetric uptake of striatal dopaminergic biomarkers, particularly in the posterior putamen with relative sparing of the caudate nucleus **(Fig. 435-3)**. These findings reflect the degeneration of nigrostriatal dopaminergic neurons and the loss of their striatal terminals. Imaging can be useful in patients where there is diagnostic uncertainty (e.g., early stage, essential tremor, dystonic tremor, psychogenic tremor) or in research studies in order to ensure accuracy, but is not necessary in routine practice. This may change in the future when there is a disease-modifying therapy and it is critically important to make a correct diagnosis as early as possible. There is also some evidence that the diagnosis of PD, and even pre-PD, may be made based on the presence of increased iron in the SNc using transcranial sonography or special MRI protocols.

FIGURE 435-3

[^{11}C]Dihydrotetrabenazine positron emission tomography (a marker of VMAT2) in healthy control (*A*) and Parkinson's disease (*B*) patient. Note the reduced striatal uptake of tracer, which is most pronounced in the posterior putamen and tends to be asymmetric. *(Courtesy of Dr. Jon Stoessl.)*



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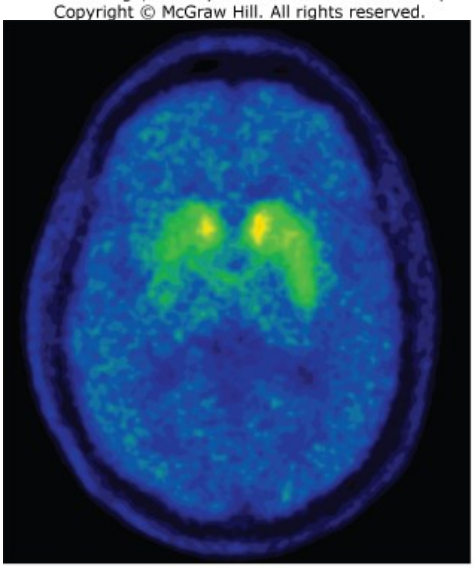

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Genetic testing can be helpful for establishing a diagnosis but is not routinely employed as monogenic forms of PD are relatively rare and likely account for no more than 10% of cases (see discussion below). A genetic form of PD should be considered in patients with a strong positive family history, early age of onset (<40 years), a particular ethnic background (see below), and in research studies. Genetic variants of the glucocerebrosidase gene (*GBA*) are the most common genetic association with PD. They are present in 5–15% of PD patients, and in 25% of Ashkenazi PD patients. However, only about 30% of people with *GBA* variants will develop PD by age 80 years. Genetic variants of the *LRRK2* gene have also attracted particular interest as they are responsible for ~1% of typical sporadic cases of the disease. LRRK2 mutations are a particularly common cause of PD (~25%) in Ashkenazi Jews and North African Berber Arabs; however, there is considerable variability in penetrance and many carriers never develop clinical features of PD. Genetic testing is of particular interest for identifying at-risk individuals in a research setting and for defining enriched populations for clinical trials of therapies directed at a particular mutation.

Atypical, Secondary, and Other Forms of Parkinsonism

Atypical parkinsonism refers to a group of neurodegenerative conditions that are usually associated with more widespread pathology than found in

PD (e.g., degeneration of striatum, globus pallidus, cerebellum, and brainstem, as well as the SNc). These conditions include multiple system atrophy (MSA; **Chap. 440**), progressive supranuclear palsy (PSP; **Chap. 432**), and corticobasal syndrome (CBS; **Chap. 432**). As a group, they tend to present with parkinsonism (rigidity and bradykinesia) but manifest clinical differences from PD reflecting their more widespread pathology. These include early involvement of speech and gait, absence of rest tremor, lack of motor asymmetry, poor or no response to levodopa, and a more aggressive clinical course. In the early stages, some cases may show a modest benefit from levodopa and can be difficult to distinguish from PD, but the diagnosis becomes clearer as the disease evolves over time. Neuroimaging of the dopamine system is usually not helpful, as striatal dopamine depletion can be seen in both PD and atypical parkinsonism. By contrast, metabolic imaging of the basal ganglia/thalamus network (using 2-F-deoxyglucose) may be helpful, showing a pattern of decreased activity in the GPi with increased activity in the thalamus, the reverse of what is seen in PD.

MSA manifests as a combination of the atypical parkinsonian features described above, as well as cerebellar and autonomic features. Clinical syndromes can be divided into a predominantly parkinsonian (MSA-p) or cerebellar (MSA-c) form. Clinically, MSA is suspected when a patient presents with features of atypical parkinsonism in conjunction with cerebellar signs and/or prominent autonomic dysfunction, usually orthostatic hypotension **(Chap. 440)**. Pathologically, MSA is characterized by degeneration of the SNc, striatum, cerebellum, and inferior olivary nuclei coupled with characteristic glial cytoplasmic inclusions (GCIs) that stain positively for α-synuclein (Lewy bodies) particularly in oligodendrocytes rather than in SNc neurons as in PD. MRI can show pathologic iron accumulation in the striatum on T2-weighted scans, high signal change in the region of the external surface of the putamen (putaminal rim) in MSA-p, or cerebellar and brainstem atrophy (the pontine "hot cross bun" sign **[Fig. 440-2]**) in MSA-c. There is currently no established evidence for any gene mutation/genetic risk factor for MSA.

PSP is a form of atypical parkinsonism that is characterized by parkinsonism as noted above coupled with slow ocular saccades, eyelid apraxia, and restricted vertical eye movements with particular impairment of downward gaze. Patients frequently experience hyperextension of the neck with early gait disturbance and falls. In later stages, speech and swallowing difficulty and cognitive impairment may become evident. Two clinical forms of PSP have been identified; a "Parkinson" form that can closely resemble PD in the early stages and can include a positive response to levodopa, and the more classic "Richardson" form that is characterized by the features described above with little or no response to levodopa. MRI may reveal a characteristic atrophy of the midbrain with relative preservation of the pons on midsagittal images (the so-called hummingbird sign). Pathologically, PSP is characterized by degeneration of the SNc, striatum, STN, midline thalamic nuclei, and pallidum, coupled with neurofibrillary tangles and inclusions that stain for the tau protein. Mutations in the MAPT gene that encodes for the tau protein have been detected in some familial cases.

CBS is a relatively uncommon condition that usually presents with asymmetric dystonic contractions and clumsiness of one hand coupled with cortical sensory disturbances manifest as apraxia, agnosia, focal limb myoclonus, or alien limb phenomenon (where the limb assumes a position in space without the patient being aware of its location or recognizing that the limb belongs to them). Dementia may occur at any stage of the disease. Both cortical and basal ganglia features are required to make this diagnosis. MRI frequently shows asymmetric cortical atrophy, but this must be carefully sought and may not be obvious to casual inspection. Pathologic findings include achromatic neuronal degeneration with tau deposits. Considerable overlap may occur both clinically and pathologically between CBS and PSP, and they may be difficult to distinguish without pathologic confirmation.

Secondary parkinsonisms occur as a consequence of other etiologic factors such as drugs, stroke, tumor, infection, or exposure to toxins (e.g., carbon monoxide, manganese) that cause basal ganglia dysfunction. Clinical features reflect the region of the basal ganglia that has been damaged. For example, strokes or tumors that affect the SNc may have a clinical picture that is largely identical to the motor features of PD, whereas toxins such as carbon monoxide or manganese that damage the globus pallidus more closely resemble atypical parkinsonism. Dopamine-blocking agents such as neuroleptics are the most common cause of secondary parkinsonism. These drugs are most widely used in psychiatry, *but physicians should be aware that drugs such as metoclopramide which are primarily used to treat gastrointestinal problems are also neuroleptic agents* and may induce secondary parkinsonism. These drugs can also cause acute and tardive dyskinesias **(see Chap. 436)**. Other drugs that can cause secondary parkinsonism include tetrabenazine, calcium channel blockers (flunarizine, cinnarizine), amiodarone, and lithium.

Parkinsonism can also be seen as a feature of dopa-responsive dystonia (DRD), a condition that results from a mutation in the *GTP-Cyclohydrolase 1* gene, which can lead to a defect in a cofactor for tyrosine hydroxylase with impairment in the manufacture of dopa and dopamine. While it typically presents as dystonia **(Chap. 436)**, it can present as a biochemically based form of parkinsonism (due to reduced synthesis of dopamine) that closely resembles PD and responds to levodopa but is not associated with abnormalities on fluoro-dopa positron emission tomography (FD-PET) nor neurodegeneration. This diagnosis should be considered in individuals aged <20 years who present with parkinsonism particularly if there are dystonic features.

Finally, parkinsonism can be seen as a feature of a variety of other neurodegenerative disorders such as Wilson's disease, Huntington's disease

(especially the juvenile form known as the Westphal variant), certain spinocerebellar ataxias, and neurodegenerative disorders with brain iron accumulation such as pantothenate kinase (PANK)–associated neurodegeneration (formerly known as Hallervorden-Spatz disease). It is particularly important to rule out Wilson's disease, as progression can be prevented with the use of copper chelators.

Some features that suggest that parkinsonism might be due to a condition other than classic PD are shown in **Table 435-3**.

TABLE 435-3

Features Suggesting an Atypical or Secondary Cause of Parkinsonism

SYMPTOMS/SIGNS	ALTERNATIVE DIAGNOSIS TO CONSIDER
History	
Early speech and gait impairment (lack of tremor, lack of motor asymmetry, early falls)	Atypical parkinsonism
Exposure to neuroleptics	Drug-induced parkinsonism
Onset prior to age 40 years	Genetic form of PD, Wilson's disease, DRD
Liver disease	Wilson's disease, non-Wilsonian hepatolenticular degeneration
Early hallucinations and dementia with later development of PD features	Dementia with Lewy bodies
Diplopia, impaired vertical gaze	PSP
Poor or no response to an adequate trial of levodopa	Atypical or secondary parkinsonism
Physical Examination	
Dementia as first or early feature	Dementia with Lewy bodies
Prominent orthostatic hypotension	MSA-p
Prominent cerebellar signs	MSA-c
Slow saccades with impaired downgaze	PSP
High-frequency (6–10 Hz) symmetric postural tremor with a prominent kinetic component	Essential tremor

Abbreviations: DRD, dopa-responsive dystonia; MSA-c, multiple-system atrophy–cerebellar type; MSA-p, multiple-system atrophy–Parkinson's type; PD, Parkinson's disease; PSP, progressive supranuclear palsy.

ETIOLOGY AND PATHOGENESIS

Most PD cases occur sporadically (~85–90%) and are of unknown cause. Gene mutations (see below) are the only known causes of PD. Twin studies performed several decades ago suggested that environmental factors might play an important role in patients with an age of onset ≥50 years, with genetic factors being more important in younger-onset patients. However, the demonstration of later-onset genetic variants (e.g., *LRRK2* and *GBA*) argues against the emphasis on environmental factors, even in individuals >50 years of age. The environmental hypothesis received some support in

the 1980s with the demonstration that MPTP (1-methyl-4-phenyl-1,2,5,6-tetrahydropyridine), a by-product of the illicit manufacture of a heroin-like drug, caused a PD syndrome in addicts in northern California. MPTP is transported into the central nervous system, where it is oxidized to form MPP^+, a mitochondrial toxin that is selectively taken up by, and damages, dopamine neurons, but typically without the formation of Lewy bodies. Importantly, MPTP or MPTP-like compounds have not been linked to sporadic PD. Epidemiologic studies have reported an increased risk of developing PD in association with exposure to pesticides, rural living, farming, and drinking well water. The solvent trichloroethylene was found to be a strong risk factor for the development of PD in U.S. Marines exposed to contaminated water at Base Camp Lejeune. Dozens of other associations have also been reported in individual studies, but results have been inconsistent, and no environmental factor has yet been proven to be a cause or contributor to PD. Some possible protective factors have also been identified in epidemiologic studies including caffeine, cigarette smoking, intake of nonsteroidal anti-inflammatory drugs, and calcium channel blockers. The validity of these findings and the responsible mechanism remain to be established.

About 10% of PD cases are familial in origin, and mutations in several PD-linked genes have been identified **(Table 435-4)**. While monogenic mutations have been shown to be causative of PD, several genetic risk factors that increase the risk of developing PD have also been identified. Large-size genome-wide association studies (GWASs) have identified more than 25 independent gene variants (single-nucleotide polymorphisms) as PD risk factors including variants in the *SNCA, LRRK2, MAPT*, and *GBA* genes as well as in the *HLA* region on chromosome 6. It has been proposed that many cases of PD may be due to a "double hit" involving an interaction between (a) one or more genetic risk factors that induce susceptibility coupled with (b) exposure to a toxic environmental factor that may induce epigenetic or somatic DNA alterations or has the potential to directly damage the dopaminergic system. In this scenario, both factors are required for PD to ensue, while the presence of either one alone is not sufficient to cause the disease. Notably, however, even if a genetic or environmental risk factor doubles the risk to develop PD, this results in a lifetime risk of only 4% or lower, and thus cannot presently be used for individual patient counseling.

TABLE 435-4

Confirmed Genetic Causes of Parkinson's Disease*

DESIGNATION* AND REFERENCE	GENEREVIEWS AND OMIM REFERENCE	CLINICAL CLUES	INHERITANCE	PREVIOUS LOCUS SYMBOL
1. Classical PD				
PARK-*SNCA*	GeneReviews *http://www.ncbi.nlm.nih.gov/books/NBK1223/* OMIM 168601	Missense mutations cause classical parkinsonism. Duplication or triplication mutations in this gene cause early-onset parkinsonism with prominent dementia.	AD	PARK1
PARK-*LRRK2*	GeneReviews *http://www.ncbi.nlm.nih.gov/books/NBK1208/* OMIM 607060	Clinically typical PD	AD	PARK8
PARK-*VPS35*	GeneReviews *http://www.ncbi.nlm.nih.gov/books/NBK1223/* OMIM 614203	Clinically typical PD	AD	PARK17
PARK-GBA	GeneReviews *http://www.ncbi.nlm.nih.gov/books/NBK1223/* OMIM 168600/606463	Clinically typical PD—possibly faster progression and greater risk of cognitive impairment	AD	
2. Early-onset PD				
PARK-*Parkin*	GeneReviews *http://www.ncbi.nlm.nih.gov/books/NBK1155/*	Often presents with dystonia, typically in a leg	AR	PARK2

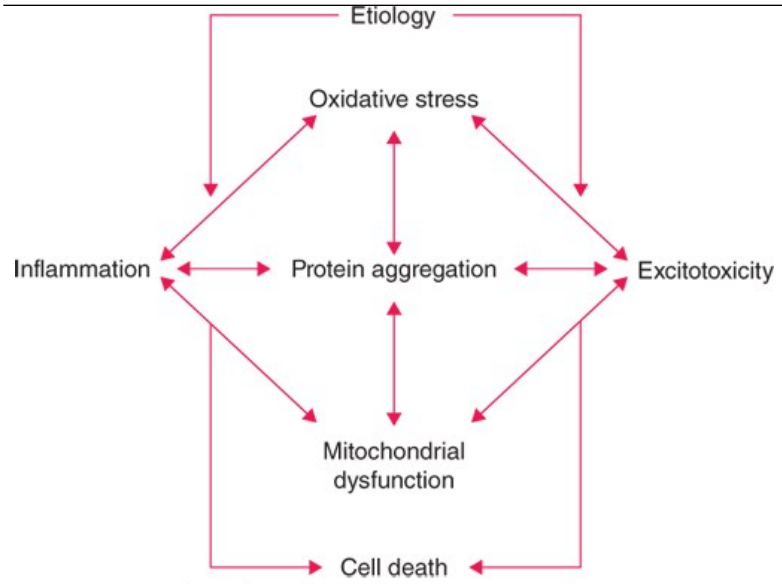
	OMIM 600116			
PARK-*PINK1*	GeneReviews *http://www.ncbi.nlm.nih.gov/books/NBK1223/* OMIM 605909	Often presents with psychiatric features	AR	PARK6
PARK-*DJ1*	GeneReviews *http://www.ncbi.nlm.nih.gov/books/NBK1223/* OMIM 606324		AR	PARK7
3. Parkinsonism				
PARK-*ATP13A2*	GeneReviews *http://www.ncbi.nlm.nih.gov/books/NBK1223/* OMIM 606693	Kufor-Rakeb syndrome with parkinsonism and dystonia; additional features: Supranuclear gaze palsy, spasticity/pyramidal signs, dementia, facial-faucial-finger mini-myoclonus, dysphagia, dysarthria, olfactory dysfunction	AR	PARK9
PARK-*FBXO7*	GeneReviews *http://www.ncbi.nlm.nih.gov/books/NBK1223/* OMIM 260300	Early-onset parkinsonism with pyramidal signs	AR	PARK15
PARK-*DNAJC6*	GeneReviews: n/a OMIM 615528	May present with mental retardation and seizures	AR	PARK19
PARK-*SYNJ1*	GeneReviews: n/a OMIM 615530	May have seizures, cognitive decline, abnormal eye movements, and dystonia	AR	PARK20

According to the recommendations of the International Parkinson's and Movement Disorder Society (C Marras: Mov Disord 31:436, 2016).

Several factors have been implicated in the pathogenesis of cell death in PD, including oxidative stress, inflammation, excitotoxicity, mitochondrial dysfunction, lysosomal/proteasomal dysfunction, and the accumulation of misfolded proteins with consequent proteolytic stress. Studies also suggest that with aging, dopamine neurons switch from sodium to calcium pacing through calcium channels, potentially making these high-energy neurons vulnerable to calcium-mediated neurotoxicity. Whatever the pathogenic mechanism, cell death appears to occur, at least in part, by way of a signal-mediated apoptotic or "suicidal" process. Each of these mechanisms offers a potential target for putative neuroprotective drugs. In addition, a role for inflammation is implicated by the genetic association of PD with the class II HLA gene *DRB1* (variants of which are associated with either protection or risk for PD), and that autoreactive T-cells recognizing peptides derived from alpha-synuclein are present in PD patients. However, it is not clear which of these factors is primary, if they are the same in all cases or specific to individual (genetic) subgroups, if they act by way of a network such that multiple insults are required for neurodegeneration to ensue, or if the findings discovered to date merely represent epiphenomena unrelated to the true cause of cell death that still remains undiscovered **(Fig. 435-4)**.

FIGURE 435-4

Schematic representation of how pathogenetic factors implicated in Parkinson's disease interact in a network manner, ultimately leading to cell death. This figure illustrates how interference with any one of these factors may not necessarily stop the cell death cascade. *(Reproduced with permission from CW Olanow: The pathogenesis of cell death in Parkinson's disease–2007. Mov Dis 22:S335, 2007.)*



Source: Joseph Loscalzo, Anthony Fauci, Dennis Kasper, Stephen Hauser, Dan Longo, J. Larry Jameson: Harrison's Principles of Internal Medicine, 21e

Although gene mutations cause only a minority of cases of PD, they have been very helpful in pointing to specific pathogenic pathways and molecular mechanisms that are likely to be central to the neurodegenerative process in the sporadic form of the disease. To date, most interest has focused on pathways implicated by mutations in α-*synuclein (SNCA)*, *GBA*, *LRRK2*, and *PINK1/Parkin*.

SNCA was the first PD-linked gene mutation and the most intensely investigated with respect to causative mutations, risk variants, as well as function of the gene and its encoded protein. Shared clinical features of patients with *SNCA* mutations include earlier age of disease onset than in nongenetic PD, a faster progression of motor signs that are mostly levodopa-responsive, early occurrence of motor fluctuations, and presence of prominent nonmotor features, particularly cognitive impairment. Intriguingly, *SNCA* constitutes the major component of Lewy bodies implicating the protein in sporadic forms of PD as well (Fig. 435-1). Importantly, duplication or triplication of the wild-type *SNCA* gene also causes PD with triplication carriers being more severely affected than carriers of duplications. These findings indicate that increased production of the normal protein alone can cause PD. Lewy pathology was discovered to have developed in healthy embryonic dopamine neurons that had been implanted into the striatum of PD patients, suggesting that the abnormal protein had transferred from affected cells to healthy unaffected dopamine neurons. Based on these findings, it has been proposed that the *SNCA* protein may be a prion, and PD a prion or prion-like disorder **(Chaps. 424 and 438)**. Like the prion protein PrP^C, *SNCA* can misfold to form β-rich sheets, join to form toxic oligomers and aggregates, polymerize to form amyloid plaques (i.e., Lewy bodies), and cause neurodegeneration with spread to involve unaffected neurons. Indeed, injection of *SNCA* fibrils into the striatum of both transgenic and wild-type rodents leads to the development of Lewy pathology in host neurons, neurodegeneration, behavioral abnormalities, and spread of *SNCA* pathology to anatomically connected sites. Further support for this hypothesis comes from the demonstration that inoculation into the striatum of homogenates derived from human Lewy bodies induces dopamine cell degeneration and widespread Lewy pathology in mice and primates. Exciting new evidence also suggests that *SNCA* pathology might begin peripherally in the enteric nervous system within the GI tract and spread by way of the vagus nerve to the lower brainstem (dorsal motor nucleus of the vagus) and ultimately to the SNc to cause the motor features of PD. There is growing interest in the possibility that the gut microbiome in PD patients causes inflammatory changes that promote alpha-synuclein misfolding and spread. The gut-brain axis might therefore offer a mechanism by which alpha-synuclein pathology might spread to the brain and cause PD, and therefore provides a novel target for therapeutic intervention.

Collectively, this evidence supports the concept that neuroprotective therapies for PD might be developed based on inhibiting the accumulation or accelerating the removal of *SNCA* aggregates, knocking down levels of host *SNCA*, preventing the spread of misfolded *SNCA*, or blocking the templating phenomenon whereby misfolded *SNCA* promotes misfolding of the native protein in a prion-like chain reaction. Many of these approaches are currently being tested in the laboratory and preliminary clinical trials have already been initiated.

Mutations in the *GBA* gene represent the most important risk factor in terms of effect size for the development of PD. *GBA* encodes for the enzyme glucocerebrosidase (GCase), which promotes lysosomal function and enhances the clearance of misfolded proteins such as *SNCA*. Experimentally, there is a direct pathophysiological link between increased levels of *SNCA* and reduced levels of *GBA*. The identification of *GBA* as a risk gene for PD

resulted from the clinical observation that patients with Gaucher's disease (GD) and their relatives commonly show signs of parkinsonism. This clinical observation led to the discovery that literally hundreds of mutations in *GBA* confer risk for the development of PD. Further, it has been shown that reduced levels of GCase activity due to *GBA* variants impair lysosomal function, which results in the accumulation of *SNCA*. Conversely, the accumulation of *SNCA* can lead to inhibition of lysosomal function and a further reduction in levels of *GBA*/GCase by interfering with endoplasmic reticulum-to-Golgi trafficking. Thus, experimentally there is a vicious cycle in which decreased *GBA* activity leads to the accumulation of *SNCA*, and increased levels of *SNCA* lead to a further impairment in lysosomal function. In this regard, it is noteworthy that lysosomal function is impaired and levels of GCase are reduced in patients with sporadic PD, and not just in those with *GBA* variants. These bidirectional effects of *SNCA* and *GBA* form a positive feedback loop that, after surpassing a theoretical threshold, could lead to self-propagating disease. These findings suggest that this molecular pathway may not only apply to patients with a *GBA* variant, but also to patients with sporadic PD or other synucleinopathies who have two normal wild-type *GBA* alleles. Some studies suggest that patients with *GBA* variants have a faster rate of progression and increased frequency of cognitive impairment. Studies of drugs that enhance GCase activity and promote lysosomal function are currently being tested in the clinic.

Multiple *LRRK2* mutations have also now been clearly linked to PD, with p.G2019S being the most common, possibly due to a founder effect in the Ashkenazi Jewish and North African Arab populations. Mutations in *LRRK2* account for 3–41% of familial PD cases (depending on the specific population) and are also found in apparently sporadic cases, albeit at a lower rate. The phenotype of *LRRK2* p.G2019S mutations is largely indistinguishable from that of sporadic PD, although tremor appears to be more common; leg tremor may be a useful diagnostic clue. The penetrance of *LRRK2* mutations is incomplete (30–74% depending on the ethnic group), and patients tend to run a more benign course. The mechanism responsible for cell death with this mutation is not conclusively known but is thought to involve enhanced kinase activity with altered phosphorylation of target proteins (including autophosphorylation) with possible impairment of lysosomal function. Kinase inhibitors can block toxicity associated with *LRRK2* mutations in laboratory models, and there has also been much interest in developing drugs directed at this target. However, nonselective kinase inhibitors are potentially toxic to the lungs and kidneys. Fortunately, *LRRK2* inhibitors have now been developed that have good preclinical safety and are currently being tested in PD populations.

Mutations in *Parkin* and *PINK1* have also been identified as a cause of PD. *Parkin* mutations are the more common, and the major cause of autosomal recessive and early-onset PD, accounting for up to 77% of cases of juvenile PD with an age of onset <20 years, and for 10–20% of early-onset PD patients in general. The disease is slowly progressive, responds well to antiparkinsonian treatment, and is commonly complicated by dystonia, but very rarely by dementia. At pathology, neurodegeneration tends to be restricted to the SNc and LC in patients with *Parkin* mutations, and Lewy bodies are typically absent. The reason for these differences from classic PD is not known but may be related to impaired ubiquitination of damaged proteins (parkin is a ubiquitin ligase that is required for Lewy body formation but may be impaired in the mutant form). The clinical phenotypes of *Parkin*- and *PINK1*-linked PD are similar. *Parkin* and *PINK1* proteins are involved in cell-protection mechanisms and in the turnover and clearance of damaged mitochondria (mitophagy). Mutations in *Parkin* and *PINK1* cause mitochondrial dysfunction in transgenic animals that can be corrected with overexpression of *Parkin*. Improving mitochondrial function is a particularly attractive potential therapeutic target because postmortem studies in PD patients show a defect in complex I of the respiratory chain in SNc neurons.

Thus, evidence is accumulating that genetic factors play an important role in both familial and "sporadic" forms of PD. It is anticipated that better understanding of the pathways responsible for cell death caused by these mutations will permit the development of more relevant animal models of PD and better-defined targets for the development of gene-specific neuroprotective drugs. A precision medicine approach in which therapies are directed specifically at patients who carry a mutation is of great interest, but it should also be appreciated that these same targets may also prove to be of importance for therapies directed at patients with sporadic PD.

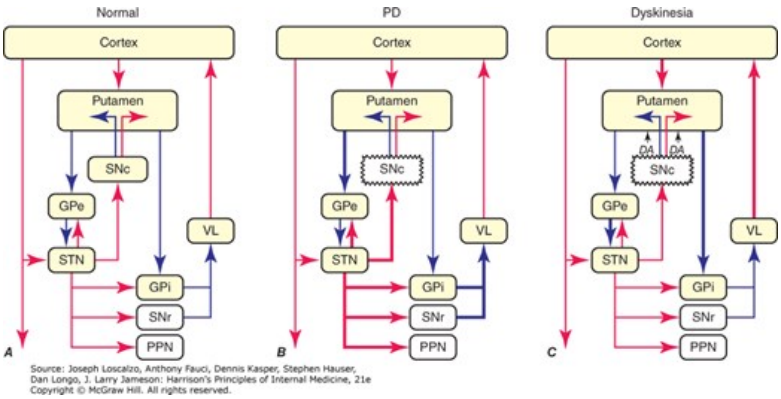
PATHOPHYSIOLOGY OF PD

The classic model of the organization of the basal ganglia in the normal and PD states is provided in **Fig. 435-5**. With respect to motor function, a series of neuronal circuits with multiple feedback and feedforward loops link the basal ganglia nuclei with corresponding cortical and brainstem motor regions in a somatotopic manner. The striatum is the major input region of the basal ganglia, while the GPi and SNr are the major output regions. The input and output regions are connected via direct and indirect pathways that have reciprocal effects on the activity of the basal ganglia output. The output of the basal ganglia provides inhibitory (GABAergic) tone to thalamic and brainstem neurons that in turn connect to motor systems in the cerebral cortex and spinal cord that control motor function. An increase in neuronal activity in the output regions of the basal ganglia (GPi/SNr) is associated with poverty of movement or parkinsonism, while decreased output results in movement facilitation and involuntary movements such as dyskinesia. Dopaminergic projections from SNc neurons serve to modulate neuronal firing and to stabilize the basal ganglia network. Normal dopamine innervation thus serves to facilitate the selection of the desired movement and to suppress or reject unwanted movements. Cortical loops

integrating the cortex and the basal ganglia are now thought to also play an important role in regulating other systems as well such as behavioral, emotional, and cognitive functions.

FIGURE 435-5

Basal ganglia organization. Classic model of the organization of the basal ganglia in the normal (***A***), Parkinson's disease (PD) (***B***), and levodopa-induced dyskinesia (***C***) state. Inhibitory connections are shown as *blue arrows* and excitatory connections as *red arrows*. The striatum is the major input region and receives its major input from the cortex. The GPi and SNr are the major output regions, and they project to the thalamocortical and brainstem motor regions. The striatum and GPi/SNr are connected by direct and indirect pathways. This model predicts that parkinsonism results from increased neuronal firing in the STN and GPi and that lesions or DBS of these targets might provide benefit. This concept led to the rationale for surgical therapies for PD. The model also predicts that dyskinesia results from decreased firing of the output regions, resulting in excessive cortical activation by the thalamus. This component of the model is not completely correct because lesions of the GPi ameliorate rather than increase dyskinesia in PD, suggesting that firing frequency is just one of the components that lead to the development of dyskinesia. DBS, deep brain stimulation; GPe, external segment of the globus pallidus; GPi, internal segment of the globus pallidus; PPN, pedunculopontine nucleus; SNc, substantia nigra, pars compacta; SNr, substantia nigra, pars reticulata; STN, subthalamic nucleus; VL, ventrolateral thalamus. *(Reproduced with permission from JA Obeso et al: Pathophysiology of the basal ganglia in Parkinson's disease. Trends Neurosci 23:S8, 2000.)*



In PD, dopamine denervation with loss of dopaminergic tone leads to increased firing of neurons in the STN and GPi, excessive inhibition of the thalamus, reduced activation of cortical motor systems, and the development of parkinsonian features (Fig. 435-5). The current role of surgery in the treatment of PD is based on this model, which predicted that lesions or high-frequency stimulation of the STN or GPi might reduce this neuronal overactivity and improve PD features. The model has proven less useful in understanding the origins of dyskinesia (see Fig. 435-5).

TREATMENT OF PARKINSON'S DISEASE

Levodopa

Since its introduction in the late 1960s, levodopa has been the mainstay of therapy for PD. Experiments in the late 1950s by Carlsson and colleagues demonstrated that blocking dopamine uptake with reserpine caused rabbits to become parkinsonian; this could be reversed with the dopamine precursor, levodopa. Subsequently, Hornykiewicz demonstrated a dopamine deficiency in the striatum of PD patients and suggested the potential benefit of dopamine replacement therapy. Dopamine does not cross the blood-brain barrier (BBB), so clinical trials were initiated with levodopa, the precursor of dopamine. Studies over the course of the next decade confirmed the value of levodopa and revolutionized the treatment of PD.

Levodopa is routinely administered in combination with a peripheral decarboxylase inhibitor to prevent its peripheral metabolism to dopamine and the development of nausea, vomiting, and orthostatic hypotension due to activation of dopamine receptors in the area postrema (the nausea and vomiting center) that are not protected by the BBB. In the United States, levodopa is combined with the decarboxylase inhibitor carbidopa (Sinemet), whereas in many other countries it is combined with benserazide (Madopar). Levodopa plus a decarboxylase inhibitor is also available in a methylated formulation, a controlled-release formulation (Sinemet CR or Madopar HP) and in combination with a catechol-*O*-methyltransferase (COMT) inhibitor (Stalevo). A long-acting formulation of levodopa (Rytary) and a levodopa carbidopa intestinal gel that is administered by continuous intraintestinal infusion via an implanted jejunal tube are also now available. An inhaled form of levodopa that is rapidly and reliably absorbed through the pulmonary alveoli has recently been approved as an on-demand therapy for the treatment of individual "off" episodes (see below).

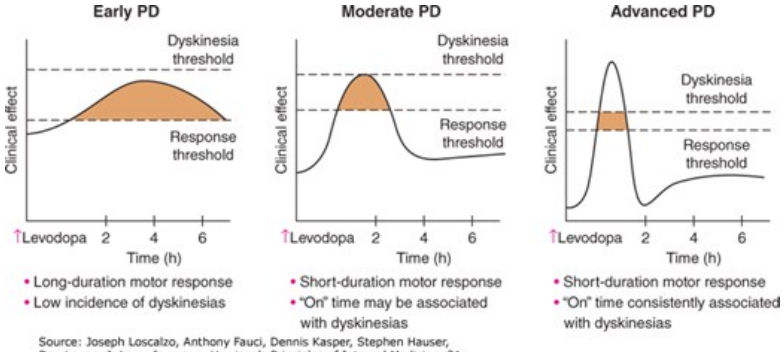
Levodopa remains the most effective symptomatic treatment for PD and the gold standard against which new therapies are compared. No current medical or surgical treatment provides antiparkinsonian benefits superior to what can be achieved with levodopa. Levodopa benefits the classic motor features of PD, prolongs independence and employability, improves quality of life, and increases life span. Indeed, levodopa also benefits some "nondopaminergic" features such as anxiety, depression, and sweating. Almost all PD patients experience improvement, and failure to respond to an adequate trial of levodopa should cause the diagnosis to be questioned.

There are important limitations of levodopa therapy. Acute dopaminergic side effects include nausea, vomiting, and orthostatic hypotension. These are usually transient and can generally be avoided by starting with low doses and gradual titration. If they persist, they can be treated with additional doses of a peripheral decarboxylase inhibitor (e.g., carbidopa), administering with food, or adding a peripheral dopamine-blocking agent such as domperidone (not available in the United States). As the disease continues to progress, features such as falling, freezing, autonomic dysfunction, sleep disorders, and dementia may emerge that are not adequately controlled by levodopa. Indeed, these nondopaminergic features (especially falls and dementia) are the primary source of disability and the main reason for hospitalization and nursing home placement for patients with advanced PD in the levodopa era.

The major concern with levodopa is that chronic levodopa treatment is associated with the development of motor complications in the large majority of patients. These consist of fluctuations in motor response ("on" episodes when the drug is working and "off" episodes when parkinsonian features return as drug wears off) and involuntary movements known as dyskinesias, which typically complicate "on" periods **(Fig. 435-6)**. When patients initially take levodopa, benefits are long-lasting (many hours) even though the drug has a relatively short half-life (60–90 min). With continued treatment, however, the duration of benefit following an individual dose becomes progressively shorter until it approaches the half-life of the drug. This loss of benefit is known as the *wearing-off effect*. Some patients may also experience a rapid and unpredictable switch from the "on" to the "off" state known as the *on-off phenomenon*. In advanced cases, because of variability in the bioavailability of standard oral levodopa, the response to a dose of levodopa may be variable and unpredictable with a given dose leading to a full-on response, a partial on-on response, a delay in turning on (delayed-on), or no response at all (no-on). Peak-dose dyskinesias can occur at the time of levodopa peak plasma concentration and maximal clinical benefit. They are usually choreiform but can manifest as dystonic movements, myoclonus, or other movement disorders. They are not troublesome when mild but can be disabling when severe, and can limit the ability to use higher doses of levodopa to better control PD motor features. In more advanced states, patients may cycle between "on" periods complicated by disabling dyskinesias and "off" periods in which they suffer from severe parkinsonism and painful dystonic postures. Patients may also experience "diphasic dyskinesias," which occur with lower plasma levodopa levels, and manifest as the levodopa dose begins to take effect and again as it wears off. These dyskinesias typically consist of transient, stereotypic, rhythmic movements that predominantly involve the lower extremities asymmetrically and are frequently associated with parkinsonism in other body regions. They can be relieved by increasing the dose of levodopa, although higher doses may induce more severe peak-dose dyskinesia and disappear as the concentration declines. Long-term double-blind studies show that the risk of developing motor complications can be minimized by using the lowest dose of levodopa that provides satisfactory benefit and through the use of polypharmacy to avoid the need for raising the dose of levodopa.

FIGURE 435-6

Changes in motor response associated with chronic levodopa treatment. Levodopa-induced motor complications. Schematic illustration of the gradual shortening of the duration of a beneficial motor response to levodopa (wearing off) and the appearance of dyskinesias complicating "on" time. PD, Parkinson's disease.



The cause of levodopa-induced motor complications is not precisely known. They are more likely to occur in younger individuals, with the use of higher doses of levodopa, in women, and in those with more severe disease. The classic model of the basal ganglia has been useful for understanding the origin of motor features in PD but has proved less valuable for understanding levodopa-induced dyskinesias (Fig. 435-5). The model predicts that dopamine replacement might excessively inhibit the pallidal output system, thereby leading to increased thalamocortical activity, enhanced stimulation of cortical motor regions, and the development of dyskinesia. However, lesions of the pallidum that dramatically reduce its output are associated with amelioration rather than induction of dyskinesia as would be suggested by the classic model. It is now thought that dyskinesia results from alterations in the GPi/SNr neuronal firing pattern (pauses, bursts, synchrony, etc.) and not simply the firing frequency alone. This leads to the transmission of "misinformation" from pallidum to thalamus/cortex that, along with firing frequency, contributes to the development of dyskinesia. Surgical lesions or high-frequency stimulation targeted at the GPi or STN presumably ameliorate dyskinesia by interfering with (blocking or masking) this abnormal neuronal activity and preventing the transfer of misinformation to motor systems.

A number of studies suggest that motor complications develop in response to nonphysiologic levodopa replacement. Striatal dopamine levels are normally maintained at a relatively constant level. In PD, where dopamine neurons and terminals have degenerated, striatal dopamine levels are dependent on the peripheral availability of levodopa. Intermittent oral doses of levodopa result in fluctuating plasma levels because of variability in the transit of the drug from the stomach to the duodenum where it is absorbed and the short half-life of the drug. This variability is translated to the brain and results in exposure of striatal dopamine receptors to alternating high and low concentrations of dopamine. This in turn has been shown to induce molecular alterations in striatal neurons, neurophysiologic changes in pallidal output neurons, and ultimately the development of motor complications. It has been hypothesized that more continuous delivery of levodopa might be more physiologic and prevent the development of motor complications. Indeed, double-blind studies have demonstrated that continuous intraintestinal infusion of levodopa/carbidopa or subcutaneous infusion of apomorphine is associated with significant improvement in "off" time and in "on" time without dyskinesia in advanced PD patients compared with optimized standard oral levodopa. These benefits are superior to what has been observed in double-blind placebo-controlled studies with other dopaminergic agents. Intestinal infusion of levodopa is approved in the United States (Duopa) and Europe (Duodopa). The treatment is, however, complicated by potentially serious adverse events related to the surgical procedure, problems related to the tubing, and the inconvenience of having to wear an infusion system. SC apomorphine infusion is approved in Europe but not yet in the United States (see below). New approaches are currently being tested in which levodopa is continuously administered by a subcutaneous route, an intraoral infusion system, or by long-acting oral levodopa formulations in an effort to avoid the need for a surgical procedure.

Behavioral complications can also be associated with levodopa treatment. A dopamine dysregulation syndrome has been described where patients have a craving for levodopa and take frequent and unnecessary doses of the drug in an addictive manner. (In this regard, it is noteworthy that cocaine binds to the dopamine uptake receptor.) PD patients taking high doses of levodopa can also develop purposeless, stereotyped behaviors such as the assembly and disassembly or collection and sorting of objects. This is known as punding, a term taken from the Swedish description of the meaningless behaviors seen in chronic amphetamine users. Hypersexuality and other impulse-control disorders are occasionally encountered with levodopa, although these are more commonly seen with dopamine agonists.

Finally, because levodopa undergoes oxidative metabolism and has the potential to generate toxic free radicals, there has been long-standing concern that, independent of the drug's ability to provide symptomatic benefits, it might accelerate neuronal degeneration. Alternatively, as levodopa improves long-term outcomes in comparison to the pre-levodopa era, it has been suggested that by restoring striatal dopamine, levodopa has the potential to have a disease-modifying or neuroprotective effect. Neither of these hypotheses has been established. A recent delayed-start study showed neither beneficial nor deleterious effects of levodopa on disease progression. Thus, it is generally recommended that levodopa be used solely based on its potential to provide symptomatic benefits balanced by the risk of inducing motor complications and other side effects.

Dopamine Agonists

Dopamine agonists are a diverse group of drugs that act directly on dopamine receptors. Unlike levodopa, they do not require metabolic conversion to an active product and do not undergo oxidative metabolism. Initial dopamine agonists were ergot derivatives (e.g., bromocriptine, pergolide, cabergoline) and were associated with potentially serious ergot-related side effects such as cardiac valvular damage and pulmonary fibrosis. They have largely been replaced by a second generation of non-ergot dopamine agonists (e.g., pramipexole, ropinirole, rotigotine). In general, dopamine agonists do not have comparable efficacy to levodopa. They were initially introduced as adjuncts to levodopa to enhance motor function and reduce "off" time in fluctuating patients. Subsequently, it was shown that dopamine agonists are less prone than levodopa to induce dyskinesia, possibly because they are relatively long-acting in comparison to levodopa. For this reason, many physicians initiate therapy with a dopamine agonist

particularly in younger patients who are more prone to develop motor complications, although supplemental levodopa is eventually required in virtually all patients. This view has been tempered by the recognition that dopamine agonists are associated with potentially serious adverse effects such as unwanted sleep episodes and impulse-control disorders (see below). Both ropinirole and pramipexole are available as orally administered immediate (tid) and extended-release (qd) formulations. Rotigotine is administered as a once-daily transdermal patch and may be useful in managing surgical patients who are not able to be treated with an oral therapy. Apomorphine is the one dopamine agonist with efficacy thought to be comparable to levodopa, but it must be administered parenterally as it is rapidly and extensively metabolized if taken orally. It has a short half-life and duration of activity (45 min). It can be administered by subcutaneous injection as a rescue agent for the treatment of severe "off" episodes but can also be administered by continuous subcutaneous infusion where it has been demonstrated to reduce both "off" time and dyskinesia in advanced patients. This latter approach has been approved in Europe but not yet in the United States. A sublingual bilayer formulation of apomorphine has recently been approved as a rapid and reliable therapy for individual "off" periods that avoids the need for a subcutaneous (SC) injection (see below).

Dopamine agonist use is associated with a variety of side effects. Acute side effects are primarily dopaminergic and include nausea, vomiting, and orthostatic hypotension. These can usually be avoided or minimized by starting with low doses and using slow titration over weeks. Side effects associated with chronic use include hallucinations, cognitive impairment, and leg edema. Sedation with sudden unintended episodes of falling asleep that can occur in dangerous situations such as while driving a motor vehicle has been reported. Patients should be informed about this potential problem and should not drive when tired. Dopamine agonists can also be associated with impulse-control disorders, including pathologic gambling, hypersexuality, and compulsive eating and shopping. Patients should be advised of these risks and specifically questioned for their occurrence at follow-up examinations. The precise cause of these problems, and why they appear to occur more frequently with dopamine agonists than levodopa, remains to be resolved, but reward systems associated with dopamine and alterations in the ventral striatum and orbitofrontal regions have been implicated. In general, chronic side effects are dose-related and can be avoided or minimized with lower doses. Injections of apomorphine can be complicated by skin lesions at sites of administration, which can be minimized by proper cleaning and alteration of the injection site. The sublingual bilayer formulation of apomorphine is associated with a relatively high frequency of oropharyngeal side effects, which are generally mild and resolve either spontaneously or with treatment withdrawal.

MAO-B Inhibitors

Inhibitors of monoamine oxidase type B (MAO-B) block central dopamine metabolism and increase synaptic concentrations of the neurotransmitter. Selegiline and rasagiline are relatively selective suicide inhibitors of the MAO-B isoform of the enzyme. Clinically, these agents provide antiparkinsonian benefits when used as monotherapy in early disease stages and reduced "off" time when used as an adjunct to levodopa in patients with motor fluctuations. MAO-B inhibitors are generally safe and well tolerated. They may increase dyskinesia in levodopa-treated patients, but this can usually be controlled by down-titrating the dose of levodopa. Inhibition of the MAO-A isoform prevents metabolism of tyramine in the gut, leading to a potentially fatal hypertensive reaction known as a "cheese effect" because it can be precipitated by foods rich in tyramine such as some cheeses, aged meats, and red wine. Selegiline and rasagiline do not functionally inhibit MAO-A and are not associated with a cheese effect with doses used in clinical practice. There are theoretical risks of a serotonin reaction in patients receiving concomitant selective serotonin reuptake inhibitor (SSRI) antidepressants, but these are rarely encountered. Safinamide (Xadago) is a reversible MAO-B inhibitor that has been approved as an adjunct to levodopa for treating advanced PD patients with motor fluctuations. The drug also acts to block activated sodium channels and inhibit glutamate release, and therefore has the potential to provide antidyskinetic as well as anti-parkinsonian effects.

Interest in MAO-B inhibitors has also focused on their potential to have disease-modifying effects. MPTP toxicity can be prevented experimentally by coadministration of a MAO-B inhibitor that blocks its oxidative conversion to the toxic pyridinium ion MPP^+ that is taken up by and selectively damages dopamine neurons. MAO-B inhibitors also have the potential to block the oxidative metabolism of dopamine and prevent oxidative stress. In addition, both selegiline and rasagiline incorporate a propargyl ring within their molecular structure that provides antiapoptotic effects in laboratory models. The DATATOP study showed that in untreated PD patients, selegiline significantly delayed the time until the emergence of disability necessitating the introduction of levodopa. However, it could not be definitively determined whether this benefit was due to a neuroprotective effect that slowed disease progression or a symptomatic effect that merely masked ongoing neurodegeneration. The ADAGIO study used a two-period delayed-start design and demonstrated that early treatment with rasagiline 1 mg/d provided benefits that could not be achieved when treatment with the same drug was initiated at a later time point, consistent with the drug having a disease-modifying effect. However, this benefit was not seen with the 2-mg dose, and it has not received regulatory approval for this indication.

Comt Inhibitors

When levodopa is administered with a decarboxylase inhibitor, it is primarily metabolized in the periphery by the catechol-*O*-methyl transferase (COMT) enzyme. Inhibitors of COMT increase the elimination half-life of levodopa and enhance its brain availability. Combining levodopa with a COMT inhibitor reduces "off" time and prolongs "on" time in fluctuating patients while enhancing motor scores. Two COMT inhibitors, tolcapone and entacapone, have been available for more than a decade; tolcapone is administered three times daily while entacapone is administered in combination with each dose of levodopa. More recently opicapone, a long-acting COMT inhibitor that requires only once-daily administration, has been approved in both Europe and the United States. A combination tablet of levodopa, carbidopa, and entacapone (Stalevo) is also available.

Side effects of COMT inhibitors are primarily dopaminergic (nausea, vomiting, increased dyskinesia) and can usually be controlled by down-titrating the dose of levodopa by 20–30% if required. Severe diarrhea has been described with tolcapone, and to a lesser degree with entacapone, and necessitates stopping the medication in 5–10% of individuals. Rare cases of fatal hepatic toxicity have been reported with tolcapone. It is still used because it is the most effective of the COMT inhibitors, but periodic monitoring of liver function is required. Liver problems have not been encountered with entacapone or opicapone. Discoloration of urine can be seen with COMT inhibitors due to accumulation of a metabolite, but it is of no clinical concern.

It has been proposed that initiating levodopa in combination with a COMT inhibitor to enhance its elimination half-life could provide more continuous levodopa delivery and reduce the risk of motor complications. While this result has been demonstrated in a preclinical MPTP model of PD, and continuous infusion reduces both "off" time and dyskinesia in advanced PD patients, no benefit of initiating levodopa with a COMT inhibitor compared to levodopa alone was detected in early PD patients in the STRIDE-PD study. This may have been because the combination was not administered at frequent enough intervals to provide continuous levodopa availability. For now, the main value of COMT inhibitors continues to be in patients who experience motor fluctuations.

Other Medical Therapies

Adenosine $A2_A$ receptor antagonists are a class of drugs that inhibit $A2_A$ receptors, which form heterodimers with D2 dopamine receptors on medium spiny striatal D2-bearing neurons of the indirect pathway. Blockade of $A2_A$ receptors decreases the excessive activation of the indirect pathway in PD and theoretically restores balance in the basal ganglia-thalamocortical circuit, providing a dopaminergic effect without the need to increase levodopa doses. These agents are generally used in combination with low doses of levodopa and provide modest anti-parkinsonian effects with a reduced risk of motor complications. Three $A2_A$ antagonists have been studied in PD but development in two has been discontinued; preladenant because it failed in phase 3 studies and tozadenant because of agranulocytosis in a few patients. Istradefylline is the only agent which is currently approved for use. Clinical trials in advanced PD patients showed improvement in "off" time comparable to other available agents but not in dyskinesia. The drug is generally well tolerated with adverse events similar to dopaminergic agents. Interestingly, caffeine is a potent $A2_A$ antagonist, and large epidemiologic studies suggest that drinking coffee is associated with a reduced frequency of PD. This has raised the question as to whether this class of agent might be neuroprotective, but this has not been established in clinical trials.

Amantadine was originally introduced as an antiviral agent but the drug was appreciated to also have antiparkinsonian effects, likely due to *N*-methyl-D-aspartate (NMDA) receptor antagonism. While some physicians use amantadine in patients with early disease for its mild symptomatic effects, it is most widely used as an antidyskinesia agent in patients with advanced PD. Indeed, it is the only oral agent that has been demonstrated in controlled studies to reduce dyskinesia without worsening parkinsonian features (indeed, motor benefits have been reported). Cognitive impairment is a major concern particularly with high doses. Other side effects include livedo reticularis and weight gain. Amantadine should always be discontinued gradually because patients can experience withdrawal-like symptoms. An extended-release formulation of amantadine has recently been approved in the United States.

Central-acting anticholinergic drugs such as trihexyphenidyl and benztropine were used historically for the treatment of PD, but they lost favor with the introduction of levodopa. Their major clinical effect is on tremor, although it is not certain that this benefit is superior to what can be obtained with agents such as levodopa and dopamine agonists. Still, they can be helpful in individual patients with severe tremor. Their use is limited particularly in the elderly, due to their propensity to induce a variety of side effects including urinary dysfunction, glaucoma, and particularly cognitive impairment.

The anticonvulsant zonisamide has also been shown to have antiparkinsonian effects and is approved for use in Japan. Its mechanism of action is unknown. Several classes of drugs are currently being investigated in an attempt to enhance antiparkinsonian effects, reduce "off" time, and treat or prevent dyskinesia. These include nicotinic agonists, glutamate antagonists, and $5\text{-}HT_{1A}$ agonists.

A list of the major drugs and available dosage strengths currently available to treat PD is provided in **Table 435-5**.

TABLE 435-5

Drugs Commonly Used for Treatment of Parkinson's Disease[a]

AGENT	AVAILABLE DOSAGES	TYPICAL DOSING
Levodopa[a]		
Carbidopa/levodopa	10/100, 25/100, 25/250 mg	200–1000 mg levodopa/day
Benserazide/levodopa	25/100, 50/200 mg	
Carbidopa/levodopa CR	25/100, 50/200 mg	
Benserazide/levodopa MDS	25/200, 25/250 mg	
Parcopa	10/100, 25/100, 25/250 mg	
Rytary (carbidopa/levodopa)	23.75/95, 36.25/145, 48.75/195, 61.25/245	See conversion tables
Carbidopa/levodopa/entacapone	12.5/50/200, 18.75/75/200, 25/100/200, 31.25/125/200, 37.5/150/200, 50/200/200 mg	
Dopamine agonists		
Pramipexole	0.125, 0.25, 0.5, 1.0, 1.5 mg	0.25–1.0 mg tid
Pramipexole ER	0.375, 0.75, 1.5. 3.0, 4.5 mg	1–3 mg/d
Ropinirole	0.25, 0.5, 1.0, 3.0 mg	6–24 mg/d
Ropinirole XL	2, 4, 6, 8 mg	6–24 mg/d
Rotigotine patch	2-, 4-, 6-, 8-mg patches	4–24 mg/d
Apomorphine SC	2–8 mg	2–8 mg
COMT inhibitors		
Entacapone	200 mg	200 mg with each levodopa dose
Tolcapone	100, 200 mg	100–200 mg tid
Opicapone	50 mg	50 mg HS
MAO-B inhibitors		
Selegiline	5 mg	5 mg bid

Rasagiline	0.5, 1.0 mg	1 mg QAM
Safinamide	100 mg	100 mg QAM
On-demand therapy for off periods		
Inhaled levodopa	5–40 mg	Up to 5 doses per day
Apomorphine sublingual strip		Up to 5 doses per day
Others		
$A2_A$ antagonist—Istradefylline	20, 40 mg	20 or 40 mg per day
Amantadine—immediate, extended-release	100–400 mg	

[a]Treatment should be individualized. Generally, drugs should be started in low doses and titrated to optimal dose.

Note: Drugs should not be withdrawn abruptly but should be gradually lowered or removed as appropriate.

Abbreviations: COMT, catechol-*O*-methyltransferase; MAO-B, monoamine oxidase type B; QAM, every morning.

On-Demand Therapies For "Off" Periods

Despite all available therapies, many patients continue to experience "off" periods. "Off" periods represent a return of parkinsonian features following the benefit of a levodopa dose administration and can be disabling for patients, causing them to be at risk for falling and choking. As noted above, taking an additional levodopa tablet does not reliably treat individual "off" episodes, and some patients may continue in the "off" state for hours despite more frequent levodopa use. This inability to reliably and rapidly treat "off" episodes causes many patients to become depressed, withdrawn, and unwilling to participate in social activities. Three therapies have now been approved as specific on-demand treatments for "off" periods: inhaled levodopa, subcutaneous injections of apomorphine, and sublingual apomorphine. Each of these avoids the variable bioavailability seen with levodopa and provides relatively predictable return to the "on" state.

Neuroprotection

Despite the many therapeutic agents available for the treatment of PD, patients continue to progress and to develop intolerable disability. A neuroprotective or disease-modifying therapy that slows or stops disease progression remains the major unmet therapeutic need. Some trials have shown positive results (e.g., selegiline, rasagiline, pramipexole, ropinirole) consistent with a disease-modifying effect. However, it has not been possible to determine with certainty if the positive results were due to neuroprotection with slowing of disease progression or confounding symptomatic or pharmacologic effects that mask disease progression. Based on genetic and laboratory findings described above, several novel targets for a putative neuroprotective therapy have been discovered and multiple candidate therapies are currently being investigated. The most exciting targets among these etiopathogenic factors include agents that interfere with *SNCA* accumulation, LRRK2 inhibitors, *GBA* and GCase enhancers and anti-inflammatory agents that inhibit activation of microglia and cytokine production. Many of these agents have already shown promise in relevant animal models of PD and are currently in clinical trials in PD patients. In patients with early PD, reducing iron accumulation in the substantia nigra using the chelator deferiprone did not improve outcomes in a large 36-week phase 2 clinical trial.

Surgical Treatment

Surgical treatments for PD have been used for more than a century. Lesions were initially placed in the motor cortex and improved tremor but were associated with motor deficits, and this approach was abandoned. Subsequently, it was appreciated that lesions placed into the ventral intermediate

(VIM) nucleus of the thalamus reduced contralateral tremor without inducing hemiparesis, but these lesions did not meaningfully help other more disabling features of PD. In the 1990s, it was shown that lesions placed in the posteroventral portion of the GPi (motor territory) improved rigidity and bradykinesia as well as tremor. Importantly, pallidotomy was also associated with marked improvement in contralateral dyskinesia. This procedure gained favor with greater understanding of the pathophysiology of PD (see above). However, this procedure is not optimal, because bilateral lesions are associated with side effects such as dysphagia, dysarthria, and impaired cognition. Lesions of the STN are also associated with antiparkinsonian benefit and reduced levodopa requirement, but there is a concern about the risk of hemiballismus, and this procedure is not commonly performed.

Most surgical procedures for PD performed today use deep brain stimulation (DBS). Here, an electrode is placed into the target area and connected to a stimulator inserted subcutaneously over the chest wall. DBS simulates the effects of a lesion without needing to make a brain lesion. The precise mechanism whereby DBS works is not fully resolved but may act by disrupting the abnormal neurophysiologic signals associated with PD and motor complications. The stimulation variables can be adjusted with respect to electrode configuration, voltage, frequency, and pulse duration in order to maximize benefit and minimize adverse side effects. The procedure does not require making a lesion in the brain and is thus suitable for performing bilateral procedures with relative safety. In cases with intolerable side effects, stimulation can be stopped and the system removed.

DBS for PD primarily targets the STN or the GPi. It provides dramatic results, particularly with respect to tremor and reducing both “off” time and dyskinesias but does not provide superior clinical benefits to levodopa. The procedure is thus primarily indicated for patients who suffer disability resulting from levodopa-induced motor complications that cannot be satisfactorily controlled with drug manipulation or those with severe tremor. Side effects can result from the surgical procedure (hemorrhage, infarction, infection), DBS system (infection, lead break, lead displacement, skin ulceration), or the stimulation itself (ocular and speech abnormalities, muscle twitches, paresthesias, depression, and rarely suicide). Recent studies indicate that benefits following DBS of the STN and GPi are comparable, but that GPi stimulation may be associated with a reduced frequency of depression. Although not all PD patients are candidates, the procedure can be profoundly beneficial for many. Long-term studies demonstrate continued benefits with respect to the classic motor features of PD, but DBS does not prevent the development of nondopaminergic features, which continue to evolve and are a source of disability. Studies continue to evaluate the optimal way to use DBS (low- vs high-frequency stimulation, closed-loop systems, etc.). Trials of DBS in early PD patients show benefits that may be superior to best medical therapy, but this must be weighed against the cost of the procedure and the risk of side effects in patients who might otherwise be well controlled with medical therapies for many years. Additionally, the PD landscape is changing with the availability of on-demand therapies for treating “off” periods and the likelihood that future therapies may provide continuous levodopa availability with reduced risk of motor complications. Controlled studies comparing DBS to other therapies aimed at improving motor function without causing dyskinesia, such as Duodopa and apomorphine infusions, remain to be performed. The utility of DBS may also be reduced in future years if new medical therapies are developed that provide the benefits of levodopa without motor complications. New targets for DBS are also being actively explored, as well as “smart” closed-loop devices that sense the patient’s need for stimulation, to provide greater benefits against gait dysfunction, depression, and cognitive impairment **(Chap. 487)**.

MRI-guided ultrasound is also now being used as a means of damaging critical target regions such as the GPi or STN in PD patients with motor complications in a noninvasive manner that avoids the needs for a surgical procedure. A recent trial demonstrated superiority of unilateral focused ultrasound ablation of GPi compared with a sham procedure, although some adverse effects such as dysarthria, worsening gait, and loss of taste were observed in some patients.

Other Experimental Therapies for PD

There has been considerable scientific and public interest in a number of novel interventions that are being investigated as possible treatments for PD. These include cell-based therapies (such as transplantation of fetal nigral dopamine cells or dopamine neurons derived from stem cells), gene therapies, trophic factors, and therapies directed against gene-specific targets. Two recent large trials of monoclonal antibodies directed against forms of α-synuclein did not show any imaging or clinical effect compared with placebo. Transplant strategies are based on the concept of implanting dopaminergic cells into the striatum to replace degenerating SNc dopamine neurons. Fetal nigral mesencephalic cells have been demonstrated to survive implantation, re-innervate the striatum in an organotypic manner, and restore motor function in PD models. However, two double-blind studies failed to show significant benefit of fetal nigral transplantation in comparison to a sham operation with respect to their primary endpoints. Additionally, grafting of fetal nigral cells is associated with a previously unrecognized form of dyskinesia (graft-induced dyskinesia) that persists after lowering or even stopping levodopa. This has been postulated to be related to suboptimal release of dopamine from grafted cells leading to a sustained form of diphasic dyskinesia. In addition, there is evidence that after many years, transplanted healthy embryonic dopamine neurons from unrelated donors develop PD pathology and become dysfunctional, suggesting transfer of α-synuclein from affected to unaffected neurons in a prion-

like manner (see discussion above). Perhaps most importantly, it is not clear how replacing dopamine cells alone will improve nondopaminergic features such as falling and dementia, which are the major sources of disability for patients with advanced disease. While stem cells, and specifically induced pluripotent stem cells (iPSCs) derived from the recipient, may overcome problems related to immunity, type and number of cells, and physiologic integration, many of these same concerns still apply. To date, stem cells have not yet been properly tested in PD patients and bear the additional concern of tumors and other unanticipated side effects. While there remains a need for scientifically based studies attempting to evaluate the potential role of cell-based therapies in PD, there is no scientific basis to warrant routine treatment of PD patients with stem cells as is being marketed in some countries.

Trophic factors are a series of proteins that enhance neuronal growth and restore function to damaged neurons. Several different trophic factors have been demonstrated to have beneficial effects on dopamine neurons in laboratory studies. Glial-derived neurotrophic factor (GDNF) and neurturin have attracted particular attention as possible therapies for PD. However, double-blind trials of intraventricular and intraputaminal infusions of GDNF failed to show benefits compared to placebo in PD patients, possibly because of inadequate delivery of the trophic molecule to the target region.

Gene therapy offers the potential of providing long-term expression of a therapeutic protein with a single procedure. Gene therapy involves placing the nucleic acid of a therapeutic protein into a viral vector that can then be taken up and incorporated into the genome of host cells and then synthesized and released on a continual basis. The AAV2 virus has been most often used as the vector because it does not promote an inflammatory response, is not incorporated into the host genome, does not induce insertional mutagenesis, and is associated with long-lasting transgene expression. Clinical trials of AAV2 delivery of the trophic factor neurturin showed promising results in open-label trials but failed in double-blind trials, even when injected into both the putamen and the SNc. Nonetheless, long-term postmortem studies have demonstrated transgene survival with biological effects as long as 10 years after treatment. Still, the degree of putaminal coverage was very small and it is likely that much higher gene doses will be required if this type of therapy is to provide positive results. Gene delivery is also being explored as a means of delivering aromatic amino acid decarboxylase with or without tyrosine hydroxylase to the striatum to facilitate the conversion of orally administered levodopa to dopamine. Animal studies suggest that this approach can provide antiparkinsonian benefits with reduced motor complications, and clinical trials in PD patients are underway. Gene therapy is also being studied as a way to enhance GBA and the gene product GCase in an attempt to promote clearance of toxic alpha synuclein. Importantly, no clinically significant adverse events have been encountered in gene therapy studies to date, but there remains a risk of unanticipated side effects. Further, it is not clear how current approaches, even if successful, will address the nondopaminergic features of the illness.

Management of rhe Nonmotor and Nondopaminergic Features of PD

Although PD treatment has primarily focused on the dopaminergic features of the illness, management of the nondopaminergic features should not be ignored. Some nonmotor features, although they likely reflect nondopaminergic pathology, nonetheless benefit from dopaminergic drugs. For example, problems such as anxiety, panic attacks, depression, pain, sweating, sensory problems, freezing, and constipation all tend to be worse during “off” periods and have been reported to improve with better dopaminergic control. Approximately 50% of PD patients suffer depression during the course of the disease, and depression is frequently underdiagnosed and undertreated. Antidepressants should not be withheld, particularly for patients with major depression, although dopaminergic agents such as pramipexole may prove helpful for both depression and PD motor features. Anxiety is also a common problem, and if not adequately managed with better antiparkinsonian control, can be treated with short-acting benzodiazepines.

Psychosis can be a problem for some PD patients and is often a harbinger of developing dementia. In contrast to AD, hallucinations are typically visual, formed, and nonthreatening. Importantly, they can limit the use of dopaminergic agents necessary to obtain satisfactory motor control. They can be associated with the use of dopaminergic drugs, and the first approach is typically to withdraw agents that are less effective than levodopa such as anticholinergics, amantadine, and dopamine agonists followed by lowering the dose of levodopa if possible. Psychosis in PD often responds to low doses of atypical neuroleptics and may permit higher doses of levodopa to be tolerated. Clozapine is an effective drug, but it can be associated with agranulocytosis, and regular monitoring is required. Quetiapine avoids these problems, but it has not been established to be effective in placebo-controlled trials. Pimavanserin (Nuplazid) differs from other atypical neuroleptics in that it is also an inverse agonist of the serotonin 5-HT_{2A} receptor. It has been shown to be effective in double-blind trials with a relatively good safety profile, and was recently approved for use in the United States.

Dementia in PD (PDD) is common, ultimately affecting as many as 80% of patients. Its frequency increases with aging and, in contrast to AD, primarily affects executive functions and attention, with relative sparing of language, memory, and calculation domains. When dementia precedes, develops coincident with, or occurs within 1 year after onset of motor dysfunction, it is by convention referred to as dementia with Lewy bodies (DLB; **Chap. 434**). These patients are particularly prone to experience hallucinations and diurnal fluctuations. Pathologically, DLB is characterized by Lewy bodies

distributed throughout the cerebral cortex (especially the hippocampus and amygdala) and is more likely to be associated with AD pathology. It is likely that DLB and PD with dementia represent a spectrum of PD rather than separate disease entities. It is notable that variants of the *GBA* gene are a significant risk factor for both PD and DLB. Mild cognitive impairment (MCI) frequently precedes the onset of dementia and is a more reliable index of impending dementia than in the general population. Indeed, many PD patients demonstrate abnormalities in cognitive testing even at the earliest stages of the disease despite having no overt clinical dysfunction. Drugs used to treat PD can worsen cognitive function and should be stopped or reduced to try to provide a compromise between antiparkinsonian benefit and preserved cognitive function. Drugs are usually discontinued in the following sequence: anticholinergics, amantadine, dopamine agonists, COMT inhibitors, and MAO-B inhibitors. Eventually, patients with cognitive impairment should be managed with the lowest dose of standard levodopa that provides meaningful antiparkinsonian effects and does not worsen mental function. Anticholinesterase agents such as memantine and cholinesterase inhibitors such as rivastigmine improve measures of cognitive function and can improve attention in PD, but do not improve cognition or quality of life in any meaningful way. More effective therapies that treat or prevent dementia are a critical unmet need in the therapy of PD.

Autonomic disturbances are common and frequently require attention. Orthostatic hypotension can be problematic and contribute to falling. Initial treatment should include adding salt to the diet and elevating the head of the bed to prevent overnight sodium natriuresis. Low doses of fludrocortisone (Florinef) or midodrine provide control for most cases. The norepinephrine precursor 3-0-methylDOPA (Droxidopa) has been shown to provide mild and transient benefits for patients with orthostatic hypotension and was recently approved by the U.S. Food and Drug Administration. Vasopressin and erythropoietin can be used in more severe or refractory cases. If orthostatic hypotension is prominent in early parkinsonian cases, a diagnosis of MSA should be considered **(Chap. 440)**. Sexual dysfunction may be helped with sildenafil or tadalafil. Urinary problems, especially in males, should be treated in consultation with a urologist to exclude prostate problems. Anticholinergic agents, such as oxybutynin (Ditropan), may be helpful. Constipation can be a very important problem for PD patients. Mild laxatives or enemas can be useful, but physicians should first ensure that patients are drinking adequate amounts of fluid and consuming a diet rich in bulk with green leafy vegetables and bran. Agents that promote gastrointestinal (GI) motility can also be helpful. Several recent studies are evaluating the effect on constipation of agents that interfere with inflammation and alpha synuclein misfolding in the GI tract.

Sleep disturbances are common in PD patients, with many experiencing fragmented sleep with excess daytime sleepiness. Restless leg syndrome, sleep apnea, and other sleep disorders also occur with increased frequency and should be treated as appropriate. REM behavior disorder (RBD) is a syndrome composed of violent movements and vocalizations during REM sleep, possibly representing acting out of dreams due to a failure of motor inhibition that typically accompanies REM sleep **(Chap. 31)**. Many PD patients have a history of RBD preceding the onset of the classic motor features of PD by many years, and most cases of RBD eventually go on to develop an α-synucleinopathy (PD or MSA). Low doses of clonazepam (0.5–1 mg at bedtime) are usually effective in controlling this problem. Consultation with a sleep specialist and polysomnography may be necessary to identify and optimally treat sleep problems. Excess daytime sleepiness can be problematic for PD patients, and therapies such as Xyrem that are effective in narcolepsy are currently being evaluated in PD.

Nonpharmacologic Therapy

Gait dysfunction with falling is an important cause of disability in PD. Dopaminergic therapies can help patients whose gait is worse in “off” times, but there are currently no specific therapies for gait dysfunction. Canes and walkers may become necessary to increase stability and reduce the risk of falling. An effective therapy for gait impairment is an important unmet need in PD.

Freezing, where patients suddenly become stuck in place for seconds to minutes as if their feet were glued to the ground, is a major cause of falling. Freezing may occur during “on” or “off” periods. Freezing during “off” periods may respond to dopaminergic therapies, but there are no specific treatments for on-period freezing and the mechanism is not well understood. Some patients will respond to sensory cues such as marching in place, singing a song, or stepping over an imaginary line or obstacle.

Speech impairment is another source of disability for many advanced PD patients. Speech therapy programs may be helpful, but benefits are generally limited and transient.

Exercise has been shown to maintain and even improve function for PD patients, and active and passive exercises with full range of motion reduce the risk of arthritis and frozen joints. Some laboratory studies suggest the possibility that exercise might also have neuroprotective effects, but this has not been confirmed in PD patients. Exercise is generally recommended for all PD patients. It is less clear that any specific type of physical therapy or exercise programs such as tai chi or dance offer any specific advantage. It is important for patients to maintain social and intellectual activities to the

extent possible. Education, assistance with financial planning, social services, and attention to home safety are important elements of the overall care plan. Information is available through numerous PD foundations and on the Internet but should be reviewed with physicians to ensure accuracy. The needs of the caregiver should not be neglected. Caring for a person with PD involves a substantial work effort and there is an increased incidence of depression among caregivers. Support groups for patients and caregivers may be useful.

Current Management of PD

The management of PD should be tailored to the needs of the individual patient, and there is no single treatment approach that is universally accepted and applicable to all individuals. Clearly, if an agent could be demonstrated to have disease-modifying effects, it should be initiated at the time of diagnosis. Indeed, recent studies suggest that dopamine terminal degeneration may be complete within 4 years of diagnosis. Epidemiologic and pathologic studies suggest that constipation, RBD, and anosmia may represent premotor features of PD and, along with imaging of the dopamine system, could permit diagnosis and the initiation of a disease-modifying therapy even prior to the onset of the classical motor features of the disease. However, no therapy has been conclusively proven to be a disease-modifying agent as yet, although rasagiline 1 mg per day met all three prespecified primary endpoints consistent with a disease-modifying effect. For now, physicians must use their judgment in deciding whether or not to introduce a drug such as rasagiline for its possible disease-modifying effects based on available preclinical and clinical information.

The next important issue to address is when to initiate symptomatic therapy and which agent to use. Several studies suggest that it may be best to start therapy at the time of diagnosis in order to preserve beneficial compensatory mechanisms and possibly provide functional benefits with improved quality of life even in the early stage of the disease. Levodopa remains the most effective symptomatic therapy for PD, and some recommend starting it immediately using low doses (≤400 mg/d), as motor complications have now clearly been shown to be dose-related. Others, however, prefer to delay introduction of levodopa treatment, particularly in younger patients, in order to reduce the risk of inducing motor complications. An alternate approach is to begin with an MAO-B inhibitor and/or a dopamine agonist, and reserve levodopa for later stages when these drugs no longer provide satisfactory control. In making this decision, the age, degree of disability, and side effect profile of the drug must all be considered. In patients with more severe disability, the elderly, and those with cognitive impairment, significant comorbidities, or in whom the diagnosis is uncertain, most physicians would initiate therapy with levodopa. Regardless of initial choice, most patients ultimately require polypharmacy (combination of levodopa, an MAO-B inhibitor, and a dopamine agonist) in order to minimize the total daily levodopa dose and reduce the risk of motor complications. While it is important to use low doses of each agent to reduce the risk of side effects, it is important not to deny patients levodopa when they cannot be adequately controlled with alternative medications. It is important to discuss the risks and benefits of the different therapeutic options with patients so that they have informed opinions as to whether they wish to start therapy and if so which drug to start.

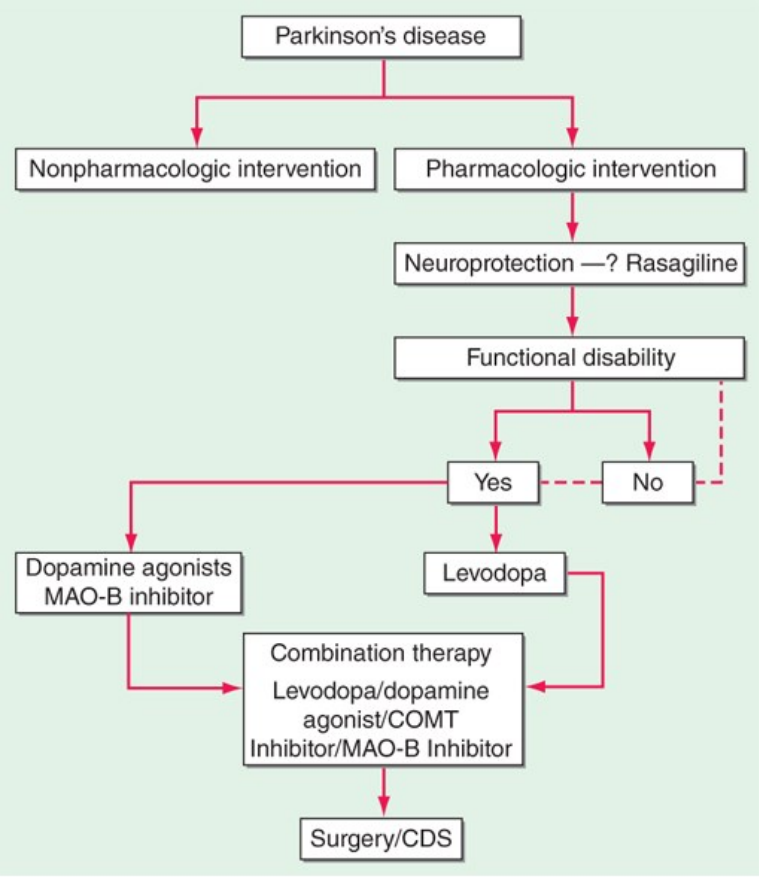
If motor complications develop, patients can initially be treated by adjusting the frequency and dose of levodopa or by combining lower doses of levodopa with a dopamine agonist, a COMT inhibitor, or an MAO-B inhibitor. More recently the $A2_A$ antagonist istradefylline has been approved in the United States as an additional medical therapy for treating “off” periods. Amantadine is the only drug that has been demonstrated to treat dyskinesia without worsening parkinsonism, but benefits may decline over time and there are important side effects related to cognitive function. In advanced cases where patients suffer motor complications that cannot be adequately controlled with medical therapies, it may be necessary to consider a surgical procedure such as DBS or Duodopa, but as described above, these procedures have their own set of complications. The use of DBS in early PD patients has been advocated by some, but there is considerable skepticism about this approach considering the costs and potential side effects, when inexpensive, well-tolerated, and effective medical alternatives are available. Continuous intraintestinal infusion of levodopa/carbidopa intestinal gel (Duodopa) offers similar benefits to DBS, but also requires a surgical intervention with potentially serious complications. Continuous infusion of apomorphine is a treatment option that does not require surgery but is associated with potentially troublesome skin nodules. Well-controlled comparative studies of these approaches are awaited. There are ongoing efforts aimed at developing systems that provide continuous delivery of levodopa or a long-acting formulation of levodopa that mirror the pharmacokinetic properties of a levodopa infusion. Such a formulation might provide all of the benefits of levodopa without motor complications and avoid the need for polypharmacy and surgical intervention. Treatment for the nonmotor features of PD should be instituted as deemed appropriate, and exercise therapy is recommended for all patients.

A decision tree that considers the various treatment options and decision points for the management of PD is provided in **Fig. 435-7**.

FIGURE 435-7

Treatment options for the management of Parkinson’s disease (PD). Decision points include: (1) Introduction of a neuroprotective therapy: no drug has been established to have or is currently approved for neuroprotection or disease modification, but there are several agents that have this

potential based on laboratory and preliminary clinical studies (e.g., rasagiline 1 mg/d, coenzyme Q10 1200 mg/d, the dopamine agonist ropinirole, and pramipexole). (2) When to initiate symptomatic therapy: There is a trend toward initiating therapy at the time of diagnosis or early in the course of the disease because patients may have some disability even at an early stage, and there is the possibility that early treatment may preserve beneficial compensatory mechanisms; however, some experts recommend waiting until there is functional disability before initiating therapy. (3) What therapy to initiate: many experts favor starting with a monoamine oxidase type B (MAO-B) inhibitor in mildly affected patients because of the good safety profile of the drug and the potential for a disease-modifying effect; dopamine agonists for younger patients with functionally significant disability to reduce the risk of motor complications; and levodopa for patients with more advanced disease, the elderly, or those with cognitive impairment. Recent studies suggest the early employment of polypharmacy using low doses of multiple drugs to avoid side effects associated with high doses of any one agent. (4) Management of motor complications: motor complications are typically approached with combination therapy to try to reduce dyskinesia and enhance the "on" time. When medical therapies cannot provide satisfactory control, surgical therapies such as DBS or continuous infusion of levodopa/carbidopa intestinal gel can be considered. (5) Nonpharmacologic approaches: interventions such as exercise, education, and support should be considered throughout the course of the disease. CDS, continuous dopaminergic stimulation; COMT, catechol-*O*-methyltransferase. *(Reproduced with permission from CW Olanow et al: The scientific and clinical basis for the treatment of Parkinson disease (2009). Neurology 72(21 Suppl 4):S1, 2009.)*



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