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triplications that manifest clinically as PD or DLB. There are multiple genes associated with PD, but mutations of glucocerebrosidase (GBA) particularly lead to PDD or DLB presentations (Chap. 446). The origins of LBD in gastrointestinal and olfactory areas suggest that environmental toxins acting on a susceptible genetic background may contribute to LBD pathogenesis (a “double-hit” hypothesis). Sev eral toxins have been associated with PD (Chap. 446), but epidemio logic studies of risk factors in DLB remain inconclusive. LABORATORY FEATURES In patients presenting with cognitive disturbances, it is always neces sary to rule out treatable causes of dementia such as drugs, infections, or metabolic disturbances (Chap. 31). Magnetic resonance imaging (MRI) of the brain can be helpful to rule out vascular parkinsonism or subdural hematomas, or support the diagnosis of other disorders such as MSA (i.e., pontine “hot-cross buns” sign; see Fig. 451-6). The biomarkers that can help diagnose LBD include the following: a polysomnogram showing RBD without atonia, seed amplification assays (SAAs) to detect αSyn in cerebrospinal fluid (CSF), demonstrating skin deposition of α-synuclein, iodine-123-meta-iodobenzylguanidine (MIBG) cardiac scintigraphy showing cardiac postganglionic sympathetic denervation, and dopamine transporter imaging using single-photon emission computed tomography (SPECT) or positron emission tomog raphy (PET) or, if associated with AD, increased CSF or blood levels of phospho-tau217 or phospho-tau181 (Table 445-1). TREATMENT Dementia with Lewy Bodies Although there are currently no disease-modifying agents to pre vent, slow, or cure LBD-related dementias, several symptomatic treatments are available. By addressing the substantial cholinergic deficit in DLB, cholinesterase inhibitors such as rivastigmine (target dose 6 mg twice daily or 9.5 mg patch daily) or donepezil (target dose 10 mg daily) often improve cognition, reduce hallucinosis, and stabilize delusional symptoms. The atypical antipsychotic pima vanserin is frequently helpful to treat the psychosis and does not worsen parkinsonism; it is approved by the U.S. Food and Drug Administration (FDA) for patients with PDD and is often used off-label for DLB. Pimavanserin (34 mg daily) is a selective inverse agonist of the serotonin 5-HT2A receptor that does not block dopa mine receptors but carries an FDA warning regarding an increase in risk of death, especially in older patients. Low-dose clozapine (begin at 6.25 mg, increasing up to 25 mg, daily) is also effective for treating hallucinations and delusions, but requires frequent blood draws due to the risk of agranulocytosis. Patients with LBD are sensitive to dopaminergic medications, which must be carefully titrated; tolerability may be improved with concomitant use of a cholinesterase inhibitor. Patients with DLB should not be exposed to typical neuroleptics, which can lead to a neuroleptic malignant syndrome and death, or anticholinergics or dopamine agonists that can exacerbate their symptoms. RBD usually responds to melatonin, requiring at times 20 mg/d. If melatonin is not effective, clonazepam, gabapentin, or codeine can be used with caution due to the possibility of worsening cogni tion or falls. Antidepressants, especially those with strong anxiolytic properties (escitalopram, paroxetine, duloxetine, or venlafaxine; see Chap. 463), are often necessary for mood and anxiety

symptoms. Orthostatic hypotension may require treatment with nonpharma cologic measures (diet high in salt and liquids, a 30° elevation of the head of the bed) or pharmacologic therapies (i.e., fludrocortisone, midodrine, droxidopa). Physical therapy can maximize motor func tion and protect against fall-related injury. Home safety assessments and transfer instruction should also be provided. Education for patients and caregivers and social worker support are also impor tant. Therefore, the care of patients with LBD requires a multidis ciplinary approach.

An experimental treatment that aims to slow down the progres sion of the disease is neflamapimod, which targets the synapse and showed promising results in initial phase 2a studies, findings that await confirmation.

The majority of caregivers for individuals with DLB are women, often spouses, who frequently experience high levels of burden and depression. The severity of behavioral symptoms, sleep dis turbances, and autonomic symptoms in the person with DLB is associated with higher caregiver burden, leading to a poorer quality of life for the caregiver. The most commonly reported caregiver concerns include the inability to plan for the future, prioritizing the needs of the person with DLB over their own, and worry about the person with DLB becoming too dependent on the caregiver, among others. Overall, caregivers expressed satisfaction with the support provided by the medical team, but they reported the lowest satisfac tion with information about disease progression and the sharing of information among medical team members. Clinicians can address caregiver needs by providing support resources, educating caregiv ers about DLB, and developing management strategies for the range of troubling symptoms experienced by patients. CHAPTER 446 ■ ■FURTHER READING Diaz-Galvan P et al: Plasma biomarkers of Alzheimer’s disease in Parkinson’s Disease the continuum of dementia with Lewy bodies. Alzheimers Dement 20:2485, 2024. Emre M et al: Clinical diagnostic criteria for dementia associated with Parkinson’s disease. Mov Disord 22:1689, 2007. Litvan I et al: Diagnostic criteria for mild cognitive impairment in Parkinson’s disease: Movement Disorder Society Task Force guide lines. Mov Disord 27:349, 2012. Mckeith IG et al: Diagnosis and management of dementia with Lewy bodies: Fourth consensus report of the DLB Consortium. Neurology 89:88, 2017. Mckeith IG et al: Research criteria for the diagnosis of prodromal dementia with Lewy bodies. Neurology 94:743, 2020. Okuzumi A et al: Propagative α-synuclein seeds as serum biomarkers for synucleinopathies. Nat Med 29:1448, 2023. Rossi M et al: Ultrasensitive RT-QuIC assay with high sensitivity and specificity for Lewy body-associated synucleinopathies. Acta Neuropathol 140:49, 2020. Sonni I et al: Clinical validity of presynaptic dopaminergic imaging with 123I-ioflupane and noradrenergic imaging with 123I-MIBG in the differential diagnosis between Alzheimer’s disease and dementia with Lewy bodies in the context of a structured 5-phase development framework. Neurobiol Aging 52:228, 2017. C. Warren Olanow*,

Anthony H. V. Schapira, Christine Klein

Parkinson’s Disease 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 physi cian James Parkinson in 1817. James Parkinson was a general physician who captured the essence of this condition based on a visual inspection *Deceased.

of a mere handful of patients, several of whom he only observed walk ing on the street and did not formally examine. It is estimated that the number of people with PD worldwide is ~10.8 million, 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 pathogenic gene mutation.

Clinically, PD is characterized by bradykinesia (slowing), rest tremor, rigidity (stiffness), and gait dysfunction with postural insta bility. These are known as the classical or “cardinal” features of PD. Additional clinical features can include freezing of gait, speech dif ficulty, swallowing impairment, and a series of nonmotor features that include autonomic disturbances, sensory alterations, mood disorders, sleep disorders, and cognitive impairment/dementia (see Table 446-1 and discussion below). Pathologically, the hallmark features of PD are degeneration of dopaminergic neurons in the substantia nigra pars compacta (SNc), reduced striatal dopamine, and intraneuronal proteinaceous inclu sions in cell bodies and axons that stain for α-synuclein (known as Lewy bodies and Lewy neurites; collectively as Lewy pathology) (Fig. 446-1). While interest has focused on the dopamine system, neuronal degeneration with Lewy pathology can also affect cholin ergic neurons of the nucleus basalis of Meynert (NBM), norepineph rine 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 PART 13 Neurologic Disorders A B FIGURE 446-1 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.

TABLE 446-1 Clinical Features of Parkinson’s Disease CARDINAL MOTOR FEATURES OTHER MOTOR FEATURES NONMOTOR FEATURES Bradykinesia Rest tremor Rigidity Postural instability Micrographia Masked facies (hypomimia) Reduced eye blinking Drooling Soft voice (hypophonia) Dysphagia Freezing Falling Anosmia Sensory disturbances

(e.g., pain, hyposmia) Mood disorders

(e.g., depression, anxiety, apathy) Sleep disturbances

(e.g., fragmented sleep, RBD) Autonomic disturbances Orthostatic hypotension Gastrointestinal disturbances Genitourinal disturbances Sexual dysfunction Cognitive impairment/dementia Abbreviation: RBD, rapid eye movement sleep behavior disorder. system. This “nondopaminergic” pathology is likely responsible for the nonmotor clinical features listed above and in Table 446-1. It has been postulated that in some cases Lewy pathology can begin in the periph eral autonomic nervous system, gastrointestinal (GI) tract, olfactory system, or dorsal motor nucleus of the vagus nerve and then spread in a predictable and sequential manner to affect the SNc and cerebral hemi spheres (Braak staging). These studies suggest that the classic degen eration of SNc dopamine neurons and the cardinal motor features of PD may develop at a mid-stage of the illness. Indeed, epidemiologic C

TABLE 446-2 Differential Diagnosis of Parkinsonism Parkinson’s disease Sporadic Genetic PD with dementia/dementia with Lewy bodies Atypical parkinsonism Multiple-system atrophy (MSA) Cerebellar type (MSA-c) Parkinson type (MSA-p) Progressive supranuclear palsy Parkinsonian variant Richardson variant Corticobasal syndrome 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) Abbreviation: MPTP, 1-methyl-4-phenyl-1,2,5,6-tetrahydropyridine. 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 represent 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. These observations have led to the notion of “body-first” and “brain-first” forms of PD based on whether pathology initially develops in the brain or periphery. Efforts are underway to accurately define the premotor stage of PD with high sensitivity and specificity. This will be of particular importance when a neuroprotective therapy becomes available as it will be desirable to initiate a disease-modifying treatment at the earliest stage of the disease possible. Recently, two new classifications have been developed aimed at defining the early stages of PD based on biological research criteria. The first stages PD based on neuronal α-synuclein accumulation. The second takes into account α-synuclein deposition, but also the distribution of neurodegen eration and pathogenic variants in known PD-causative genes. ■ ■DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS Parkinsonism is a term that is used to define a syndrome manifest by bradykinesia with rigidity and/or tremor. The differential diagnosis includes PD, atypical parkinsonisms such as multiple-system atrophy (MSA) and progressive supranuclear palsy (PSP), secondary parkinson ism, and parkinsonism associated with other neurodegenerative condi tions in which parkinsonian features are present (see Table 446-2 and discussion below). These conditions affect the basal ganglia, 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. 446-2). They differ, however, in the precise site of involvement within the basal Striatum (Putamen and Caudate) Globus Pallidus Globus Pallidus SNc A B FIGURE 446-2 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.

Other neurodegenerative disorders 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 CHAPTER 446 ganglia, the specific pathologic characteristics, and the clinical picture. 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 rigid ity) 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 patients. Imaging of the dopamine system and new biomarkers (see below) further

increase diagnostic accuracy. The International Parkinson's Disease and Movement Disorder Society (MDS) has proposed 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 introduced. While motor parkinsonism has been retained as the core feature of the disease, in these criteria, the specific diagnosis of PD 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. in "Further Reading"). Parkinson's Disease Imaging of the brain dopamine system can be helpful in diagnos ing PD and is performed using positron emission tomography (PET) or single-photon emission computed tomography (SPECT). These studies typically show reduced and asymmetric uptake in the stria tum, particularly in the posterior putamen with relative sparing of the caudate nucleus (Fig. 446-3). These findings reflect the degeneration Striatum Globus Pallidus STN SNc

A PART 13 Neurologic Disorders B FIGURE 446-3 [11C]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.) of nigrostriatal dopaminergic neurons and the loss of their striatal terminals. Imaging is useful in patients where there is diagnostic uncertainty (e.g., early-stage disease, essential tremor, dystonic tremor, psychogenic tremor) or in research studies in order to ensure diagnos tic accuracy, but it is not routinely required in clinical practice. This may change in the future when a disease-modifying therapy becomes available and it becomes critically important to make a correct diagno sis as early as possible. There is also some evidence suggesting that a diagnosis of PD, and even prodromal PD, may be made based on the presence of increased iron in the SNc using transcranial sonography or special magnetic resonance imaging (MRI) protocols. There have been intensive efforts to image α-synuclein in the brain but, in con trast to beta-amyloid or tau imaging in Alzheimer's disease, this has proven difficult as most of the abnormal α-synuclein protein is located within cells. This makes it difficult to develop a marker that binds to α-synuclein and that can be detected with imaging. There has been a longstanding interest in developing a biomarker for PD that could aid in diagnosis, differentiate PD from other parkinsonian conditions, potentially assess the effects of a putative disease-modifying therapy, and be used as an endpoint in clinical trials. Considerable interest has focused on detecting abnormal α-synuclein deposits in cerebrospinal fluid (CSF), blood, muscle, and other tissues, but results to date have been inconsistent. The development of the α-synuclein seeding amplification assay (SAA) has provided a novel means to support a clinical diagnosis of PD. The SAA was developed for use on CSF and skin and provides a binary result indicating the presence or absence of endogenous α-synuclein sufficient to result in aggregation upon addition of α-synuclein "seeds." This assay has very high sensitivity and specificity and is able to distinguish PD from other parkinsonisms. At present, the test has been primarily applied

in a research setting, but the development of a blood-based assay may extend its use into a clinical role. This assay also has the potential to permit diagnosis in early-stage and even prodromal PD. Genetic testing can be helpful for establishing a diagnosis but is not routinely employed as monogenic forms of PD are relatively uncom mon and account for only 5% of cases, although this

increases to 15% when pathogenic variants in the strongest known risk gene, glucocer ebrosidase (GBA1), are included (see discussion below), and this num ber may increase as more knowledge is acquired. A genetic form of PD should be considered in patients with a strong positive family history, early age of onset (<40 years), and a particular ethnic background (see below), and in research studies. Genetic variants of GBA1 are the most common genetic association with PD. They are present in ~10% of PD patients and in 25% of Ashkenazi PD patients. However, only ~20–30% of people with GBA1 variants will develop PD, and PD risk is correlated with the severity of the variant effect. Pathogenic variants in the LRRK2 gene have also attracted particular interest as they are responsible for ~3% 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 ~40–50% of carriers never develop clinical features of PD. Interestingly, some PD cases associated with LRRK2 mutations and other genetic causes have been described without Lewy bodies. 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 pathogenic mutation or pathway. Atypical, Secondary, and Other Forms of Parkinsonism

Atypical parkinsonism refers to a group of neurodegenerative condi tions that are usually associated with more widespread pathology than found in PD (e.g., degeneration potentially involving the striatum, globus pallidus, cerebellum, and brainstem as well as the SNc). These conditions include MSA (Chap. 451), PSP (Chap. 443), and cortico basal syndrome (CBS) (Chap. 443). As a group, they tend to present with parkinsonism (rigidity and bradykinesia) but manifest clinical differences from PD, reflecting their different pathologies. Clinical fea tures that typically differ from classical PD 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. They can be difficult to distinguish from PD in the early stages where levodopa has not yet been tried and in some cases that show a modest benefit from levodopa, but the diagnosis usually becomes clear 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 varying degrees of cerebellar and autonomic features. Clinical syndromes can be divided into a predomi nantly parkinsonian (MSA-p), cerebellar (MSA-c), and more rarely, a primary autonomic form. Clinically, MSA is suspected when a patient has features of atypical parkinsonism in conjunction with cerebellar signs and/or prominent autonomic dysfunction, usually orthostatic hypotension and a poor or absent response to levodopa (Chap. 451). The use of biomarkers (e.g., SAA) has increased the accuracy of diag nosis in the early stages of the disease, and the rate of progression is typically more aggressive than in classic PD. 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 aggregates (Lewy bodies), which accumulate 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. 451-6]) in MSA-c. There is currently no established evidence

for any gene mutation or genetic risk factor for MSA, and no specific treatment exists. PSP is characterized by the features noted above coupled with slow ocular saccades, eyelid apraxia, and restricted vertical eye movements with 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 resembles 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 mid sagittal 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 encoding 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 on 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 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 clini cal picture that is very similar to PD, whereas toxins such as carbon monoxide or manganese that damage the globus pallidus more closely resemble atypical parkinsonism and have a poor response to levodopa. 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 metoclo pramide, which are primarily used to treat GI problems, are also neuro leptic agents and may induce secondary parkinsonism. These drugs can also cause acute and tardive dyskinesias (see Chap. 447). 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 dysto nia (DRD), a condition that typically results from pathogenic variants in the GTP-cyclohydrolase 1 gene, which 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. 447), it can present as a biochemically based form of parkinsonism (due to reduced synthesis of dopamine) closely resembling PD. DRD patients respond to levodopa, but abnormalities on fluorodopa PET (FD-PET) are typically not seen, nor are drug-induced dyskinesias, reflecting a biochemical abnormality without degeneration of the underlying anatomic structures. DRD 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 (Chaps. 427 and 447), Huntington’s disease (especially the juvenile form known as the Westphal variant) (Chap. 447), certain spinocerebellar ataxias (Chap. 450), and neurodegenerative disorders with brain iron

accumu lation such as pantothenate kinase (PANK)–associated neurodegenera tion (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.

TABLE 446-3 Features Suggesting an Atypical or Secondary Cause of Parkinsonism ALTERNATIVE DIAGNOSIS TO CONSIDER SYMPTOMS/SIGNS 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 Hallucinations and dementia which precede the development of PD features Dementia with Lewy bodies CHAPTER 446 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 Parkinson's Disease 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. Some features that suggest that parkinsonism might be due to a condition other than classic PD are shown in Table 446-3. ■ ■ETIOLOGY AND PATHOGENESIS Most PD cases occur sporadically and are of unknown cause. Gene mutations (see below) are the only known causes of PD and may be found even in seemingly sporadic cases. Twin studies performed several decades ago suggested that environmental factors may 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 genetic variants (e.g., LRRK2 and GBA1) causing later onset PD shows that certain monogenic forms can manifest as late as in the eighth or ninth decade. With the advent of new sequenc ing technologies (long-read sequencing), numerous monogenic causes of late-onset neurodegenerative diseases have recently been identi fied, such as intronic repeat expansions in the FGF14 gene causing late-onset ataxia (Chap. 450), and it is conceivable that additional monogenic forms of PD will also be identified with this technology. In addition, it is likely that genetic factors could modify age at onset and severity of both genetic and nongenetic forms of PD. The environmental hypothesis received some support in the 1980s with the demonstration that MPTP (1-methyl-4-phenyl-1,2,5,6tetrahydropyridine), a by-product of the illicit manufacture of a heroin-like drug, caused a PD syndrome in addicts in northern Cali fornia. 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 com pounds have not been linked to sporadic PD. Epidemiologic studies have reported an increased risk of developing PD in association with exposure to pesticides, solvents, rural living, farming, and drinking well water, but study results have been inconsistent. Additionally, doz ens of other associations have also been reported in individual studies. To date, no environmental factor has yet been proven to be a cause of 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.

Large studies show that about 15% of PD cases are familial in ori gin, and mutations in several PD-linked genes have been identified (Table 446-4). While uncommon pathogenic variants in PD genes (i.e., mutations) have been shown to be causative of PD or to contribute to PD risk, a plethora of common genetic variants—alone or in combina tion as part of polygenic risk scores—are associated with an increased risk of developing PD. These include variants in the SNCA, LRRK2, MAPT, and GBA1 genes and may be ethnicity-specific, such as a strong risk variant confined to the African or African-admixed population. It has been proposed that many cases of PD may be due to a “double hit” involving an interaction between (1) one or more genetic risk factors that induce susceptibility and (2) 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, two factors (or more) are required for PD to ensue, while the presence of either one alone is not sufficient to cause the disease. While the “double-hit” hypothesis is of interest, there is no direct evidence for its support at this time. Furthermore, even if a genetic or environmen tal risk factor doubles the risk of developing PD, this only results in a lifetime risk of 4–6% or lower, and thus cannot presently be used for individual patient counseling. PART 13 Neurologic Disorders Thus, the bulk of accumulating evidence suggests that genetic fac tors play an important role in both familial and “sporadic” forms of PD, while the role of environmental factors remains unsettled. Although TABLE 446-4 Confirmed Genetic Causes of Parkinson’s Disease (PD) with a Clinical Presentation Similar to Idiopathic PDa DESIGNATIONa AND REFERENCE GENEREVIEWS AND OMIM REFERENCE CLINICAL CLUESB COMMENTS Dominantly Inherited PD PARK-SNCA GeneReviews http://www.ncbi.nlm.nih.gov/books/NBK1223/ OMIM 168601 Median AAO: 46 years (range 19–77 years); 25th/75th percentile: 36/54 years. Gene duplications cause classical PD. Most missense mutations and triplications cause early-onset, severe parkinsonism with prominent cognitive dysfunction PARK-LRRK2 GeneReviews http://www.ncbi.nlm.nih.gov/books/NBK1208/ OMIM 607060 Median AAO: 56 years (range 20–95 years); 25th/75th percentile: 47/64 years. Clinically typical PD with slightly slower progression PARK-VPS35 GeneReviews http://www.ncbi.nlm.nih.gov/books/NBK1223/ OMIM 616710 Median AAO: 52 years (range 26–75 years); 25th/75th percentile: 45/61 years. Clinically typical PD PARK-CHCHD2 GeneReviews N/A OMIM 614203 Likely clinically typical PD. Systematic MDSGene review not yet available PARK-RAB32 GeneReviews N/A OMIM 612906 (disease link not yet included) Likely clinically typical PD, possibly more frequent dementia. Systematic MDSGene review not yet available PARK-GBA1 GeneReviews http://www.ncbi.nlm.nih.gov/books/NBK1223/ OMIM 168600/606463 Clinically overall typical PD; however, faster progression and greater risk of cognitive impairment. Systematic MDSGene review not yet available Recessively Inherited PD PARK-PRKN GeneReviews http://www.ncbi.nlm.nih.gov/books/NBK1155/ OMIM 600116 Median AAO: 31 years (range 3–81 years); 25th/75th percentile: 23/38 years. Often presents with dystonia, typically in a leg PARK-PINK1 GeneReviews http://www.ncbi.nlm.nih.gov/books/NBK1223/ OMIM 605909 Median AAO: 32 years (range 9–67 years); 25th/75th percentile: 24/40 years. Prominent psychiatric features have been described in several families PARK-PARK7 GeneReviews http://www.ncbi.nlm.nih.gov/books/NBK1223/ OMIM 606324 Median AAO: 27 years (range 15–40 years); 25th/75th percentile: 22/34 aAccording to the recommendations of the International Parkinson’s and Movement Disorder Society (C Marras et al: Mov Disord 31:436, 2016; and L Lange et al: Mov Disord 37:905, 2022). bAdapted from MDSGene (www.mdsgene.org). Abbreviations: AAO, age at onset; N/A, not applicable; OMIM, Online Mendelian Inheritance in Man; PD, Parkinson’s disease.

mutations in PD genes identified to date cause only a minority of cases of PD, they have been very helpful in pointing to specific targets, pathways, and molecular mechanisms that are likely to be central to the neurodegenerative process in the sporadic form of the disease. Detailed clinical and genetic features of monogenic PD are available in the MDSGene database (www.mdsgene.org). The α-synuclein gene (SNCA) was the first to be linked to PD and is also the most intensely investigated with respect to causative mutations, risk variants, function, and role in the etiopathogenesis of PD. 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. Importantly, duplication or triplica tion of the wild-type SNCA gene also causes PD, with triplication car riers being more severely affected than carriers of duplications. These findings indicate that increased production of the normal protein alone can cause PD. Intriguingly, α-synuclein constitutes the major component of Lewy bodies, implicating the protein in sporadic forms of PD as well (Fig. 446-1). In a remarkable study, 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 α-synuclein protein may be a prion and PD a prion disorder (Chaps. 435 and 449). In this model, α-synuclein can misfold Very rare form of PD, α-synuclein protein main component of Lewy bodies, the pathological hallmark of PD Most common known genetic form of PD Very rare form of PD Very rare form of PD, predominantly found in Asia Most recently found form of PD. All currently identified patients and families carry the same founder pathogenic variant Strongest known genetic risk factor for PD; incomplete penetrance Most common early-onset form of genetic PD. Protein name: Parkin Clinically very similar to PARK-PRKN but much rarer Clinically very similar to PARK-PRKN and PARK-PINK1, but rarest of all forms. Protein name: DJ-1

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 unaffected neurons. Indeed, injec tion of purified α-synuclein fibrils into the striatum of both transgenic and wild-type rodents produced Lewy pathology in host neurons, neu rodegeneration, behavioral abnormalities, and spread of α-synuclein 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. Evidence also suggests that in some cases α-synuclein pathology might begin peripherally 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 (the Braak hypothesis). There is also interest in the possibility that the gut microbiome in PD patients can cause inflammatory changes that promote α-synuclein misfolding with spread to the brain via the vagus nerve. The gut-brain axis might therefore offer a mechanism by which α-synuclein pathology could spread to the brain and cause PD. The prion hypothesis for PD represents an exciting, although still unproven, line of investigation. Multiple lines of evidence support the concept that neuroprotective therapies for PD might be developed based on inhibiting the accumula tion or accelerating the removal of toxic forms of α-synuclein, knock ing down levels of host SNCA to prevent their misfolding, preventing the spread of misfolded SNCA, or blocking the templating phenom enon whereby misfolded α-synuclein promotes misfolding of the native protein in a prion-like chain reaction. Numerous studies testing dif ferent approaches to targeting α-

synuclein are ongoing. Interestingly, postmortem studies in PD patients who had undergone a transplant procedure observed that inflammation with activated microglia at the transplant site preceded the development of α-synuclein aggregates by many years. This suggests the possibility that a chronic inflammatory milieu could promote misfolding of host α-synuclein, leading to neuro degeneration; to date, however, immune-based approaches to clearing α-synuclein have not been successful in PD. Pathogenic variants of the GBA1 gene represent the most important risk factor in terms of both the development of PD and its severity. GBA encodes the enzyme glucocerebrosidase (GCase), which pro motes lysosomal function and enhances the clearance of misfolded α-synuclein. The identification of GBA1 as a risk for PD resulted from the clinical observation that patients with Gaucher's disease (GD) and their relatives show features of parkinsonism more frequently than would be expected. This clinical observation led to the discovery that literally hundreds of variants in GBA1 confer risk for the develop ment of PD. Experimentally, it has been shown that reduced levels of GCase activity due to GBA variants impair lysosomal function, resulting in the accumulation of α-synuclein. Conversely, the accumu lation of α-synuclein leads to inhibition of lysosomal function and a further reduction in levels of GCase by interfering with endoplasmic reticulum-to-Golgi trafficking. Thus, there is a vicious cycle in which decreased GCase activity leads to the accumulation of α-synuclein, and increased levels of α-synuclein lead to impairment in lysosomal func tion. 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 GBA1 variants. These findings suggest that this molecular pathway may not only apply to patients with a GBA1 vari ants but also to patients with sporadic PD or other synucleinopathies who have normal wild-type GBA1 alleles. Some studies suggest that patients with certain GBA1 variants (e.g., L444P) have a faster rate of progression and an increased frequency of cognitive impairment. Drug and gene-based therapies that enhance GCase activity and promote lysosomal function are currently being tested in the clinic as putative neuroprotective therapies. Multiple LRRK2 pathogenic mutations have also been clearly linked to PD; p.G2019S is the most common, possibly due to a founder effect in the Ashkenazi Jewish and North African Arab populations. Pathogenic variants in LRRK2 account for 2–41% of familial PD cases (depending on the specific population) and are also found in

apparently sporadic cases, albeit at a lower rate. More than 200 variants have been reported. Recently developed functional assays testing acti vation of kinase activity as a gain-of-function effect help distinguish causative variants from those of uncertain significance. The phenotype of LRRK2 p.G2019S mutations is largely indistinguishable from that of sporadic PD, although tremor appears to be more common and disease progression is slightly slower than in idiopathic PD. The penetrance of LRRK2 pathogenic variants is incomplete (30–74% depending on the ethnic group), and patients tend to run a more benign course, with less cognitive impairment than seen in idiopathic PD. The mechanism responsible for cell death with this mutation is likely due to enhanced kinase activity with altered phosphorylation of target proteins (includ ing autophosphorylation) with possible impairment of lysosomal function. In laboratory models, kinase inhibitors can block toxicity associated with LRRK2 pathogenic variants. Accordingly, there has been 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 with and without pathogenic LRRK2 variants. There has been particular interest in c-Abl inhibitors, which target the tyrosine residue on α-synuclein protein and potentially prevent conversion to a toxic

species. A pathogenic variant in RAB32 has been identified as a novel form of dominantly inherited PD with incomplete penetrance. Interestingly, LRRK2 and RAB32 interact directly, thus representing another potentially druggable target.

CHAPTER 446 Parkinson’s Disease Pathogenic variants in PRKN, PINK1, and PARK7 have also been identified as a cause of PD. PRKN mutations are the most common and the major cause of autosomal recessive early-onset PD, accounting for up to 77% of juvenile PD patients, 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 com monly complicated by dystonia, but rarely by dementia. Pathologically, neurodegeneration tends to be restricted to the SNc and LC in patients with PRKN mutations, and Lewy bodies are only present in ~20% of the brains. The reason for these differences from classic PD is not known but may be related to the fact that parkin is a ubiquitin ligase and ubiquitination of damaged proteins is required for their clearance and possibly for their incorporation into Lewy bodies. The clinical phenotypes linked to pathogenic variants in PRKN, PINK1, and PRK7 are indistinguishable from one another. Parkin and PINK1 proteins are involved in cell protection mechanisms related to the turnover and clearance of damaged mitochondria (mitophagy). Indeed, mutations in Parkin and PINK1 cause mitochondrial dysfunction in transgenic animals that can be corrected with overexpression of parkin. Improv ing mitochondrial function is another attractive therapeutic target as postmortem studies in PD patients show a defect in complex I of the respiratory chain in SNc neurons. Several factors have been implicated in the pathogenesis of cell death in PD, including oxidative stress, inflammation, excitotoxicity, mitochondrial dysfunction, and lysosomal/proteasomal dysfunction. Inflammation and altered immunity have also been implicated as potentially key factors in the degenerative process. Genetic studies demonstrate an association of PD with the class II human leukocyte antigen (HLA) gene DRB1 (variants of which are associated with either protection or risk for PD) and findings in monogenic forms of PD demonstrating a role of inflammation and the immune sys tem. As noted above, this is supported by pathologic studies dem onstrating that inflammation occurs years before the accumulation of α-synuclein aggregates in transplanted patients, suggesting that inflammation plays a triggering role. Altered immunity has also been suggested by studies showing that autoreactive T cells recognizing peptides derived from α-synuclein are present in PD patients. Further, drugs such as sargramostim that upregulate T-regulatory cells have shown positive results in studies in animal models, and early studies in PD patients are underway. 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; however, clinical

Etiology Oxidative stress Protein aggregation Excitotoxicity Inflammation Mitochondrial dysfunction PART 13 Neurologic Disorders Cell death FIGURE 446-4 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. Movement Disorders 22:S-335, 2007.) studies to date have not conclusively demonstrated a benefit using therapies directed against any of these targets. Moreover, it is not clear which of these factors is primary, if they are the same in all cases or specific to individual 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. 446-4). It is anticipated that a better understanding of the pathways involved in the etiology and pathogenesis of cell death in PD will permit the development of more relevant animal models and better-defined tar gets for the development of neuroprotective drugs. Normal PD Dyskinesia Cortex Putamen SNc SNc SNc GPe GPe VL STN STN GPi SNr PPN A B C FIGURE 446-5 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 input from the motor regions of the cerebral 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 striatal pathways whose neurons are D1- and D2-bearing, respectively. This model predicts that parkinsonism results from decreased dopamine inhibition of the indirect pathway, leading to increased neuronal firing in the STN and GPi with inhibition of thalamocortical firing. These observations suggested that lesions or DBS of these targets might provide antiparkinsonian benefit. 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 and that other components of the neuronal firing pattern such as pauses and bursts are also important. 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. (Derived from JA Obeso et al: Trends Neurosci 23:S8, 2000.)

■ ■PATHOPHYSIOLOGY OF PD The classic model of the organization of the basal ganglia in the normal and PD states is provided in Fig. 446-5. With respect to motor function, a series of neuronal circuits with multiple feedback and feedforward loops link the basal ganglia nuclei with correspond ing cortical and brainstem motor regions in a somatotopic manner. The striatum is the major input region of the basal ganglia, whereas the GPi and substantia nigra (SNr) are the major output regions. The input and output regions are connected via direct and indirect pathways that have reciprocal effects on basal ganglia activity and motor function. The output of the basal ganglia provides inhibitory (GABAergic) tone to modulate excitatory 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 reduced thalamic activity and poverty of move ment or parkinsonism, while decreased output results in movement facilitation. Dopaminergic projections from SNc neurons serve to modulate neuronal firing (in both directions) and thus to stabilize the basal ganglia network. Normal dopamine innervation thus serves to facilitate the selection of the desired movement and suppression or rejection of unwanted movements. Cortical loops integrating the cortex and the basal ganglia are thought to also play an important role in regulating other systems, such as behavioral, emotional, and cognitive functions. 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. 446-5). 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 their

inhibition of thalamocortical pathways and thus improve PD features. This model has not proven to be as valuable in under standing dyskinesia where benefits are also seen with lesions in these regions (see below) and where it is now thought that that dyskinesia arises from altered firing patterns and not just firing frequency. Cortex Cortex Cortex Putamen Putamen DA DA GPe VL VL STN GPi GPi SNr SNr PPN PPN

■ ■COVID-19 AND PD SARS-CoV-2 viral infection can worsen PD features and off time. In addition, having PD increases the risks of complications and death rate associated with having a SARS-CoV-2 infection. Interestingly, it has been shown that the SARS-CoV-2 virus can enter the brain and cause inflammation with microglial activation, and new-onset cases of PD have been reported following infection. In this regard, it raises similarities to PD cases associated with the influenza A epidemic in 1918. Home confinement due to the risks of acquiring SARS-CoV-2 infection has also altered conduct of clinical trials in PD patients and promoted “remote” clinical trials in which patients are evaluated online rather than in person. With validation of the reliability of this approach, it is likely that remote clinical trials will be increasingly employed in routine clinical trials of PD patients. TREATMENT Parkinson’s Disease LEVODOPA Since its introduction in the late 1960s, levodopa has been the main stay of therapy for PD. Experiments in the late 1950s by Carlsson and colleagues demonstrated that blocking dopamine uptake with reser pine 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 ther apy. Dopamine does not cross the blood-brain barrier (BBB), so clinical trials were initiated with levodopa, the precursor of dopa mine. 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 metab olism 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 meth ylated formulation, a controlled-release formulation (Sinemet CR or Madopar HP), and in combination with a catechol-O-methyl transferase (COMT) inhibitor (Stalevo). A long-acting formulation of levodopa (Rytary), a levodopa-carbidopa intestinal gel adminis tered continuously by intra-intestinal infusion, continuous subcu taneous infusions of a levodopa formulation, and an inhaled form of levodopa that is absorbed through the pulmonary alveoli are also now available (see below). Levodopa remains the most effective symptomatic treatment for PD and the gold standard against which new therapies are compared. Early PD Dyskinesia threshold Clinical effect Clinical effect Response threshold

Time (h) ↑Levodopa

Time (h) ↑Levodopa • Long-duration motor response • Low incidence of dyskinesias • Short-duration motor response • “On” time may be associated with dyskinesias FIGURE 446-6 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.

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 up-titration. If they persist, they can be treated with additional doses of a peripheral decarboxylase inhibitor (e.g., carbidopa) or administered with food or 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 place ment for patients with advanced PD in the levodopa era. CHAPTER 446 Parkinson’s Disease The major concern with levodopa is that chronic treatment with ongoing disease progression is associated in most patients with the development of motor complications. Motor complica tions consist of fluctuations in motor response (“on” episodes when the drug is working and “off” episodes when Parkinsonian features return as the drug wears off) and involuntary movements known as dyskinesias, which typically complicate “on” periods (Fig. 446-6). When patients initially take levodopa, benefits are long-lasting (many hours and to some degree even weeks—the “long-duration” response) 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 pro gressively shorter until benefits approach 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 an individual dose of levodopa may be variable and unpredictable with the patient experiencing a full-on response, a partial-on response, a delay in turning on (delayed-on), or no response at all (no-on). Peak-dose dyskinesias 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 Moderate PD Advanced PD Dyskinesia threshold Dyskinesia threshold Clinical effect Response threshold Response threshold

Time (h) ↑Levodopa • Short-duration motor response • “On” time consistently associated with dyskinesias

and “off” periods in which they suffer from severe parkinson ism 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 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.

The precise cause of levodopa-induced motor complications is not known. They are more likely to occur in younger individuals, with the use of higher doses of levodopa, in females, 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, as noted above, but has proven less valuable for understanding levodopa-induced dyskinesias (Fig. 446-5). The model predicts that dopamine replacement might excessively inhibit the pallidal out put system, thereby leading to increased thalamocortical activity, enhanced stimulation of cortical motor regions, and the develop ment of dyskinesia. However, lesions of the pallidum that dramati cally 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, which along with firing frequency contributes to the development of dyskinesia. Surgical or ultrasound lesions or high-frequency stimulation tar geted at the GPi or STN presumably ameliorate dyskinesia by inter fering with (blocking or masking) this abnormal neuronal activity and preventing the transfer of misinformation to motor systems. PART 13 Neurologic Disorders A number of studies suggest that motor complications develop in response to nonphysiologic levodopa replacement. Striatal dopa mine 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 the short half-life of the drug and variability in the transit of the drug from the stomach to the jejunum where it is absorbed. These fluctuations are also reflected in the brain and result in striatal dopamine receptors being exposed to alternating pathologically 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 or reduce the fre quency of motor complications. Indeed, double-blind studies in PD patients have demonstrated that continuous intraintestinal infusion of levodopa/carbidopa and continuous subcutaneous infusion of apomorphine or levodopa are associated with significant improve ment in “off” time and in “on” time without troublesome dyskinesia, compared with intermittent doses of standard oral levodopa. These benefits are superior to those observed in placebo-controlled stud ies with other dopaminergic agents. Intestinal infusion of levodopa is approved in the United States and Europe (Duodopa, Duopa). The treatment can, however, be 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. Continuous subcutaneous delivery of levodopa or apomor phine avoids the need for a surgical procedure but is associated with a high frequency of cutaneous lesions and still requires wearing the inconvenient pump system. These are approved in Europe but not yet in the United States.

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 assem bly 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 occasion ally encountered with levodopa but 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 con cern 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 (explained below) showed neither beneficial nor deleterious effects of levodopa on the rate of clinical progression. Thus, it is generally recommended that levodopa be used solely based on its potential to provide symptom atic 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 meta bolic conversion to an active product and do not undergo oxidative metabolism. Initial dopamine agonists were ergot derivatives (e.g., bromocriptine, pergolide) and were associated with potentially seri ous 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 dopa mine 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 initiated 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 (three times a day) and extended-release (once a day) formulations. Rotigotine is administered as a once-daily transder mal 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 subcu taneous 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 shown to reduce both "off" time and dyskinesia in advanced patients. A sublingual bilayer formulation of apomorphine has 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 nau sea, vomiting, and orthostatic hypotension. These can usually be

avoided or minimized by starting with low doses and slowly uptitrating 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 dan gerous situations, such as while driving a motor vehicle, have 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 differential effects on reward systems associated with dopamine and alterations in the ventral striatum and orbitofrontal regions have been implicated. In general, chronic side effects are doserelated and can be avoided or minimized with lower doses. Injec tions of apomorphine can be complicated by skin lesions at sites of administration, which can be minimized by proper cleaning and alternating the injection sites. The sublingual bilayer formulation of apomorphine can be associated with oropharyngeal side effects, but these are generally mild and resolve either spontaneously or with treatment withdrawal. A selective D1 agonist has been developed and shown to have mild antiparkinsonian effects but not greater than those seen with other available dopamine agonists. MAO-B INHIBITORS Inhibitors of monoamine oxidase type B (MAO-B) block cen tral dopamine MAO-B-oxidative metabolism and thereby 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 antiparkin sonian 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 levodopatreated 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. Currently available MAO-B inhibitors are selective, do not functionally inhibit the MAO-A enzyme, and are not associated with a cheese effect with doses used in clinical prac tice. There are theoretical risks of a serotonin reaction in patients receiving concomitant selective serotonin reuptake inhibitor (SSRI) antidepressants, but these are rarely encountered. Safinamide is a reversible and selective 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 poten tial to provide antidyskinetic as well as ant-parkinsonian effects. Interest in MAO-B inhibitors has also focused on their potential to have disease-modifying effects (see below). COMT INHIBITORS When levodopa is administered with a decarboxylase inhibitor, it is primarily metabolized in the periphery by the COMT enzyme. Inhibitors of COMT block its peripheral metabolism, 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. The 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. Opicapone, a long-acting COMT inhibitor that only requires once-daily administration, has more recently been approved in both Europe and the United States. A combination tab let of levodopa, carbidopa, and entacapone (Stalevo) is also available.

Side effects of COMT inhibitors are primarily dopaminer gic (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 tox icity 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 encoun tered 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 (see below). 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 combina tion was not administered at frequent enough intervals to provide continuous levodopa availability. For now, the main value of COMT inhibitors continues to be as an adjunct to levodopa. CHAPTER 446 Parkinson’s Disease OTHER MEDICAL THERAPIES Adenosine A2A receptor antagonists are a class of drugs that inhibit A2A receptors that form heterodimers with D2 dopamine receptors on medium spiny striatal D2-bearing neurons of the indirect path way. Blockade of A2A 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 and activate D1-receptor-bearing neurons that comprise the direct pathway. Three A2A 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 that is currently approved for use. Clinical trials in advanced PD patients showed improve ment 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 A2A antagonist, and 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 neuroprotec tive, but this has not been established in clinical trials. Amantadine was originally introduced as an antiviral agent, but the drug was observed to also have antiparkinsonian effects, likely due to antagonism of the N-methyl-d-aspartate (NMDA) recep tor. 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 demonstrated in controlled studies to reduce dyskinesia without worsening parkinsonian features (indeed, motor benefits have been reported to be improved). 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 also been developed. 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 supe rior to what can be obtained with agents such as levodopa and dopa mine 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.

TABLE 446-5 Drugs Commonly Used for Treatment of Parkinson’s Diseasea AGENT AVAILABLE DOSAGES TYPICAL DOSING Levodopaa 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 25/200, 25/250 mg MDS Parcopa 10/100, 25/100, 25/250 mg Rytary (carbidopa/ 23.75/95, 36.25/145, 48.75/195, 61.25/245 12.5/50/200, 18.75/75/200, 25/100/200, 31.25/125/200, 37.5/150/200, 50/200/200 mg See conversion tables levodopa) Carbidopa/levodopa/ entacapone PART 13 Neurologic Disorders 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 Opicapone 100, 200 mg 50 mg 100–200 mg tid 50 mg HS MAO-B inhibitors Selegiline 5 mg 5 mg bid Rasagiline Safinamide 0.5, 1.0 mg 100 mg 1 mg QAM 100 mg QAM On-demand therapy for off periods Inhaled levodopa Apomorphine sublingual

5–40 mg

Up to 5 doses per day Up to 5 doses per day strip Others A2A antagonist—

20, 40 mg

20 or 40 mg/d Istradefylline Amantadine—immediate, 100–400 mg extended-release aTreatment 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. The anticonvulsant zonisamide has also been shown to have mild antiparkinsonian effects and is approved for use in Japan. Its mechanism of action is unknown. Several classes of drugs are cur rently being investigated in an attempt to enhance antiparkinsonian effects, reduce “off” time, and treat or prevent dyskinesia. These include a selective inhibitor of the GPR6 receptor, which is local ized to D2-bearing striatal neurons, and a selective antagonist of the D3 receptor. A list of the major drugs and available dosage strengths currently available to treat PD is provided in Table 446-5. CONTINUOUS DOPAMINERGIC DELIVERY As noted above, there is evidence suggesting that motor complica tions are related to nonphysiologic restoration of brain DA with intermittent oral doses of short-acting levodopa formulations. To overcome these problems, several approaches have been developed to deliver levodopa in a more continuous manner. These include

continuous intraintestinal and continuous subcutaneous delivery. Each of these has been shown to provide more stable plasma levodopa levels than intermittent doses of standard levodopa and to be associated with reduced “off” time and increased “on” time with out troublesome dyskinesia. Similar results have also been seen with continuous subcutaneous delivery of apomorphine, as well as con tinuous oral delivery using a small intraoral micropump attached to a retainer. Attempts continue to develop an oral formulation of levodopa that can provide relatively continuous plasma levodopa levels and avoid a surgical procedure with resulting risk for cutane ous nodules and

abscesses and the need to wear an inconvenient and cumbersome infusion pump. ON-DEMAND THERAPIES FOR OFF PERIODS Despite all available therapies including continuous delivery, many patients still experience “off” periods. Off periods can be disabling for patients, placing them 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 a levodopa dose. This inability to reliably and rapidly treat off episodes causes many patients to become depressed, withdrawn, and unwilling to participate in social or business activities. Three therapies have now been approved as specific on-demand treatments for off periods: inhaled levodopa, subcutaneous injection of apomorphine, and sublingual apomor phine. Each of these is fast acting, avoids the variable bioavailability seen with standard oral levodopa, and provides a predictable return to the on state. NEUROPROTECTION Despite the many therapeutic agents available for the symptomatic treatment of PD, patients continue to progress and to develop intol erable 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 neu roprotection with slowing of disease progression or confounding symptomatic or pharmacologic effects that mask disease progres sion. Interest has focused on selegiline and rasagiline, as MPTP toxicity can be prevented experimentally by coadministration of an MAO-B inhibitor. These agents block the oxidative conversion of MPTP to the pyridinium ion MPP+ that is taken up by and selec tively 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. In the classic DATATOP study, selegiline delayed the time until the emergence of disability necessitating the introduction of levodopa in untreated PD patients. However, it could not be defini tively 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 tested the putative neuroprotective effects of rasagiline using a two-period delayed-start design. In the first period, patients are randomized to treatment with the active drug or placebo. In the second period, patients in both groups receive the active treat ment. If early treatment provides an enduring benefit that cannot be achieved with delayed treatment, the result is consistent with a disease-modifying effect. In ADAGIO, early treatment with rasagi line 1 mg/d provided significant benefits that could not be achieved when treatment with the same drug was initiated at a later time point, consistent with a disease-modifying effect. However, this benefit was not seen with the 2-mg dose, and it did not receive regu latory approval for this indication. The reason the 2-mg dose failed remains uncertain, but many physicians use rasagiline in early-stage patients based on its potential to have neuroprotective effects.

Neuroprotective therapies that prevent the formation or accu mulation of toxic α-synuclein species, inhibit LRRK2, or enhance GCase are currently being studied. GLP-1 agonists, developed for use in diabetes, have also shown some promise based on antiinflammatory and pro-mitochondrial actions, but results in doubleblind studies have been inconsistent. 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 thala mus 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 rigid ity 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 proce dure is not optimal because PD affects both sides of the body and 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 understood but may act by disrupting the abnormal neu rophysiological signals that are associated with PD and motor com plications. 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 where there are no benefits or with intolerable side effects, stimulation can be stopped and the system removed. DBS for PD is primarily used to target the STN or the GPi. It provides antiparkinsonian benefits, particularly with respect to tremor, and reduces both “off” time and dyskinesias but does not provide antiparkinsonian benefits that are superior to levodopa. The procedure is thus primarily indicated for patients who suffer disability from severe tremor or from levodopa-induced motor complications that cannot be satisfactorily controlled with drug adjustments. Side effects can result from the surgical procedure (hemorrhage, infarction, infection), the DBS system (infection, lead break, lead displacement, skin ulceration), or the stimulation itself (ocular and speech abnormalities, muscle twitches, paresthesias, depression, and rarely suicide). Results of DBS of the STN and GPi are comparable, but 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 the appropriate patient. Long-term studies demonstrate continued benefits with respect to the dopaminergic features of PD, but DBS does not prevent the development of nondopaminergic features, which continue to evolve as the disease progresses and are a source of disability. Studies continue to evaluate the optimal way to use DBS (e.g., low- vs high-frequency stimulation, closed loop systems, adaptive approaches). Trials of DBS in early PD patients show ben efits 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 relatively safe medical therapies for many years especially if used correctly (see below). 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 a reduced risk of motor complications. Controlled studies comparing DBS to other therapies aimed at improving motor function without causing dyskinesia, such as continuous intraintestinal or SC levodopa infusions, remain to be performed. The utility of DBS may also be reduced in the future if new medi cal therapies are developed that provide the benefits of levodopa without motor complications. New targets for DBS are also being actively explored directed at gait dysfunction,

depression, and cog nitive impairment, as well as “smart” closed-loop devices that sense the patient’s need for stimulation (Chap. 500).

MRI-guided ultrasound is also now being used to target critical regions such as the GPi or STN in PD patients with motor compli cations in a relatively noninvasive manner that avoids the needs for a surgical procedure. Preliminary results suggest good target local ization and safety. Ultrasound has also been used to interrupt the BBB in a specific location, which might facilitate access to the brain for therapies that otherwise might not cross the BBB. CHAPTER 446 OTHER EXPERIMENTAL THERAPIES FOR PD These include cell-based therapies (e.g., transplantation of dopa mine neurons derived from stem cells), gene therapies, and trophic factors. Transplant strategies are based on the concept of implant ing 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. Grafting of fetal nigral cells is associated with a previously unrec ognized 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 discus sion above). There are also concerns about immune reactions to the injection of foreign tissue. Stem cells, and specifically autologous induced pluripotent stem (IPS) cells derived from the recipient, may overcome problems related to immune reactions and physi ologic integration, but many of the concerns listed above still apply. To date, stem cells have not yet been properly tested in double-blind studies and bear the additional theoretical concern of malignant transformation and other unanticipated side effects. Importantly, it is not clear how replacing dopamine cells alone will improve the nondopaminergic features of PD such as falling and dementia, which are the major sources of disability for patients with advanced disease. While there remains a need for scientifically based studies to evaluate the potential role of cell-based therapies in PD, there is no basis for treating PD patients with stem cells in nonresearch studies, as is being marketed in some countries. Parkinson’s Disease Trophic factors are a series of proteins that enhance neuronal growth and potentially could restore function to damaged neurons. Based on laboratory studies, several different trophic factors appear to have beneficial effects on dopamine neurons, and glial-derived neurotrophic factor (GDNF) and neurturin have attracted particu lar attention as possible therapies for PD. However, double-blind trials of intraventricular and intraputaminal infusions of GDNF failed to benefit PD patients, possibly because of inadequate deliv ery 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. AAV2 delivery of the trophic factor neurturin (a member of the GDNF family) showed promis ing

results in open-label trials but also failed in double-blind trials, even when injected into both the putamen and the SNc. Nonethe less, long-term postmortem studies have demonstrated transgene survival with biological effects as long as 10 years after treatment. However, 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 clinically meaningful results.

Gene delivery is also being explored as a means of deliver ing aromatic amino acid decarboxylase with or without tyrosine hydroxylase into 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; clinical trials in PD patients are underway. Gene therapy is also being studied as a way to enhance GBA1 and the gene product GCase in an attempt to promote lysosomal clear ance of misfolded α-synuclein protein. PART 13 Neurologic Disorders Importantly, no clinically significant adverse events have been encountered in gene therapy studies directed at the central ner vous system to date, but there remains a risk of unanticipated side effects including mutagenesis. Further, it is not clear how current approaches directed at the dopamine system, even if successful, will address the nondopaminergic features of the illness. MANAGEMENT OF NONMOTOR AND NONDOPAMINERGIC FEATURES OF PD Although PD treatment has primarily focused on the dopaminergic features of the illness, management of the nondopaminergic fea tures should not be ignored. Some nonmotor features 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. Recent studies with light therapy suggest that exposure to the specific light frequencies can restore a more normal circadian rhythm (which is altered in PD) and provide both motor and nonmotor benefits, particularly with respect to sleep and mood. Approximately 50% of PD patients suffer depression during the course of the disease, and depression is frequently underdiag nosed and undertreated. Antidepressants should not be withheld, particularly for patients with major depression, although dopami nergic agents such as pramipexole may prove helpful for treating both depression and PD motor features. Anxiety is also a common problem, and if not adequately controlled with antiparkinsonian therapies, it 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 in PD patients are typically visual, formed, and nonthreatening. Importantly, they can be associated with the use of dopaminergic drugs and may limit the use of these agents required for satisfactory motor control. Initial management is 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 neu roleptics and may permit higher doses of levodopa to be tolerated. Clozapine is an effective drug, but it can be associated with agranu locytosis, 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 an inverse agonist and antagonist of the serotonin 5-HT2A receptor. It has been shown to be effective in short-term double-blind trials but has only mild efficacy (although it can be very effective in individual patients) and has been reported to be associated with QT prolongation and death in elderly patients. 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 or develops within 1 year after onset of motor dysfunction, it is by convention referred to as dementia with Lewy bodies (DLB; Chap. 445). Interestingly, if dementia develops in a PD patient after 12 months, it is referred to as PD dementia, although it is not clear that these represent different disease entities. 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 notable that variants of the GBA1 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 as it occurs in the setting of a neurodegenerative disor der. Indeed, many PD patients demonstrate abnormalities in cogni tive 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 and pro vide a compromise between antiparkinsonian benefit and preserved cognitive function. Drugs are usually discontinued in the follow ing 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 riv astigmine 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 con tribute 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-methylDOPS (Droxidopa) has been shown to provide mild but transient benefits for patients with orthostatic hypotension. 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. 451). 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. Anti cholinergic 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 GI motility can also be helpful. Several studies are evaluating the effect on constipation of agents that interfere with inflammation and α-synuclein misfolding in the GI tract. Sleep disturbances are common in PD patients, with many expe riencing fragmented sleep with excess daytime sleepiness. These can be severe and result in sudden-onset sleep episodes that may occur in dangerous situations such as while driving a car. These problems tend to be exaggerated by dopamine agonists, particularly in high doses. These problems may relate to alterations in circadian rhythm associated with degeneration in melanopsin-containing neurons in the retina and cells of the suprachiasmatic nucleus, which occur in PD patients. Recent studies suggest that both motor and nonmotor features may be improved with light therapy using specific wavelengths that restore circadian rhythm in PD patients. Restless leg syndrome, sleep apnea, and other sleep disorders also occur with increased frequency in PD and should be treated as appropriate. REM behavior disorder (RBD) is a syndrome com posed 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. 33). 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 even tually 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 sodium oxybate (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 may be of help for patients whose gait is worse in “off” time, 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 sec onds to minutes as if their feet were glued to the ground, is another important problem and 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 help 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 program, such as tai chi or dance, offers 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 web but should be reviewed with physi cians 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 or even in the premotor stage once that can be diagnosed with confidence. Recent studies suggest that striatal dopamine terminal degeneration may be com plete within 4 years of diagnosis and thus limit the potential benefit of a therapy started after that time, even if it has been shown to have protective effects. Epidemiologic and pathologic studies sug gest that constipation, RBD, and anosmia may represent premotor features of PD and, along with imaging of the dopamine system and biomarkers (see above), could permit diagnosis and the initiation of a disease-modifying therapy prior to the onset of the classical motor features of the disease. However, no therapy has yet been conclusively proven to be a disease-modifying agent, although as noted above, rasagiline 1 mg/d met all three prespecified primary endpoints consistent with

such a benefit. 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 symp tomatic 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 effec tive symptomatic therapy for PD, and the American Academy of Neurology recommends starting it immediately using low doses (≤400 mg/d), as motor complications have now clearly been shown to be dose-related. Other experts, however, prefer to delay intro duction of levodopa treatment, particularly in younger patients, in order to reduce the risk of inducing motor complications. An alternate approach is to begin with am 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 deci sion, the patient's age, degree of disability, and the side effect profile of the drug must all be considered. In patients with more severe dis ability, the elderly, and those with cognitive impairment, significant comorbidities, or uncertain diagnosis, most physicians would initi ate therapy with levodopa. A new pill that combines very low doses of rasagiline and pramipexole in extended-release formulations has been developed that provides clinical benefits comparable to highdose pramipexole in higher doses but without sleep-related and dopaminergic side effects. As such, it could represent an alternative to levodopa as initial therapy for PD.

CHAPTER 446 Parkinson's Disease Regardless of initial choice, most patients ultimately benefit from polypharmacy (a combination of levodopa, an MAO-B inhibi tor, 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, patients should not be denied levodopa when they cannot be adequately controlled with alternative medications. It is also important to discuss the risks and benefits of the different therapeutic options with patients so that they have informed opin ions as to whether they wish to start therapy early 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 inhibi tor, or an MAO-B inhibitor. An A2A antagonist such as istrade fylline is an additional therapy that can be used 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 particularly with higher doses. On-demand therapies such as subcutaneous apomorphine, inhaled levodopa, and sublingual apomorphine can be used to treat individual off periods and can delay the need for surgery in some patients. In advanced cases where patients suffer motor complications that can not be adequately controlled with medical therapies, it may be nec essary to consider a surgical procedure such as DBS or a continuous dopaminergic therapy such as Duodopa or subcutaneous infusion of levodopa or apomorphine, but as described above, these proce dures 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 ben efits to DBS, but also requires a surgical intervention with poten tially serious complications. Continuous subcutaneous infusion of levodopa or apomorphine does not require surgery but is associ ated with potentially troublesome

skin nodules and abscesses and requires wearing an inconvenient infusion pump during the course of the day and potentially around the clock. Comparative studies of these approaches are awaited. There are ongoing efforts aimed at developing a long-acting formulation of levodopa that mirrors the pharmacokinetic properties of a levodopa infusion. Such a formu lation might provide all of the benefits of levodopa without motor

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