Parkinson Disease

HOW TO RECEIVE CREDIT

- Read the enclosed course.
- Complete the questions at the end of the course.
- Return your completed Evaluation to NetCE by mail or fax, or complete online at www.NetCE.com. (If you are a physician, behavioral health professional, or Florida nurse, please return the included Answer Sheet/Evaluation.) Your postmark or facsimile date will be used as your completion date.
- Receive your Certificate(s) of Completion by mail, fax, or email.

Faculty

John M. Leonard, MD, Professor of Medicine Emeritus, Vanderbilt University School of Medicine, completed his postgraduate clinical training at the Yale and Vanderbilt University Medical Centers before joining the Vanderbilt faculty in 1974. He is a clinician-educator and for many years served as director of residency training and student educational programs for the Vanderbilt University Department of Medicine. Over a career span of 40 years, Dr. Leonard conducted an active practice of general internal medicine and an inpatient consulting practice of infectious diseases.

Faculty Disclosure

Contributing faculty, John M. Leonard, MD, has disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

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The division planners and director have disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

Audience

This course is designed for all healthcare providers in the primary care setting who may encounter patients with Parkinson disease.

Accreditations & Approvals

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A complete Works Cited list begins on page 50.

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Successful completion of this CME activity, which includes participation in the activity with individual assessments of the participant and feedback to the participant, enables the participant to earn 10 MOC points in the American Board of Pediatrics' (ABP) Maintenance of Certification (MOC) program. It is the CME activity provider's responsibility to submit participant completion information to ACCME for the purpose of granting ABP MOC credit.

This activity has been designated for 10 Lifelong Learning (Part II) credits for the American Board of Pathology Continuing Certification Program.

Through an agreement between the Accreditation Council for Continuing Medical Education and the Royal College of Physicians and Surgeons of Canada, medical practitioners participating in the Royal College MOC Program may record completion of accredited activities registered under the ACCME's "CME in Support of MOC" program in Section 3 of the Royal College's MOC Program.

NetCE designates this continuing education activity for 10 ANCC contact hours.

IPCE CREDIT™

This activity was planned by and for the healthcare team, and learners will receive 10 Interprofessional Continuing Education (IPCE) credits for learning and change.

NetCE designates this continuing education activity for 12 hours for Alabama nurses.

NetCE designates this continuing education activity for 5 pharmacotherapeutic/pharmacology contact hours.

AACN Synergy CERP Category A.

NetCE designates this activity for 5 hours ACPE credit(s). ACPE Universal Activity Numbers: JA4008164-0000-25-XXX-H01-P and JA4008164-0000-25-XXX-H01-T.

Social workers completing this intermediate-to-advanced course receive 10 Clinical continuing education credits.

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In addition to states that accept ANCC, NetCE is approved as a provider of continuing education in nursing by: Alabama, Provider #ABNP0353 (valid through 07/29/2025); Arkansas, Provider #50-2405; California, BRN Provider #CEP9784; California, LVN Provider #V10662; California, PT Provider #V10842; District of Columbia, Provider #50-2405; Florida, Provider #50-2405; Georgia, Provider #50-2405; Kentucky, Provider #7-0054 (valid through 12/31/2025); South Carolina, Provider #50-2405; West Virginia, RN and APRN Provider #50-2405.

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About the Sponsor

The purpose of NetCE is to provide challenging curricula to assist healthcare professionals to raise their levels of expertise while fulfilling their continuing education requirements, thereby improving the quality of healthcare.

Our contributing faculty members have taken care to ensure that the information and recommendations are accurate and compatible with the standards generally accepted at the time of publication. The publisher disclaims any liability, loss or damage incurred as a consequence, directly or indirectly, of the use and application of any of the contents. Participants are cautioned about the potential risk of using limited knowledge when integrating new techniques into practice.

Disclosure Statement

It is the policy of NetCE not to accept commercial support. Furthermore, commercial interests are prohibited from distributing or providing access to this activity to learners.

Course Objective

The purpose of this course is to provide physicians, nurses, and other members of the interprofessional healthcare team a review of pathogenesis, disease progression, diagnosis, and management of Parkinson disease, in order to improve patient care and quality of life.

Learning Objectives

Upon completion of this course, you should be able to:

1. Outline the history of Parkinson disease (PD) and scientific developments related to recognition of the disease.
2. Integrate epidemiologic considerations, risk factor assessment, and defining clinical features into a framework for evaluating a patient with suspected Parkinson disease.
3. Assess motor and non-motor symptoms and signs in relation to pathophysiology of PD.
4. Anticipate the time course of symptom development in patients with PD, and use this to assess clinical probability and to inform follow-up of a patient in whom the diagnosis is unclear.
5. Refine history and clinical examination skills in order to detect the early motor and non-motor signs and symptoms of PD.
6. Develop a strategy for the initial workup of patients with suspected PD that conforms with diagnostic and clinical staging criteria.
7. Compare and contrast syndromes that may mimic PD and their differential diagnosis.
8. Devise a treatment strategy and select an appropriate drug regimen for the management of PD.
9. Create an approach to the management of PD based on stage of the disease, severity of symptoms, and rate of progression.
10. Discuss the role of non-motor symptoms of PD and devise a strategy for treatment.
11. Outline a long-term plan for monitoring the course of illness, including patient and family education and safety precautions.

Pharmacy Technician Learning Objectives

Upon completion of this course, you should be able to:

1. Outline the history, epidemiology, and clinical signs/symptoms of Parkinson disease (PD) and scientific developments related to recognition of the disease.
2. Describe the assessment and management of PD.

Sections marked with this symbol include evidence-based practice recommendations. The level of evidence and/or strength of recommendation, as provided by the evidence-based source, are also included so you may determine the validity or relevance of the information. These sections may be used in conjunction with the course material for better application to your daily practice.

INTRODUCTION

Parkinson disease (PD) is a chronic, slowly progressive neurodegenerative disease affecting approximately 1% of adults older than 60 years of age [1; 2]. Advances in the understanding of PD pathophysiology have improved recognition of both non-motor and motor symptoms that characterize each stage of disease progression, which in turn facilitates early diagnosis and therapeutic intervention. Timely diagnosis and the application of therapeutic options tailored to the disease stage promotes a better quality life for patients with PD [3; 4]. As a chronic illness, patients with PD benefit from regular follow-up with their primary care provider working in concert with a neurology consultant and an interprofessional care team. Important aspects of care include need to adjust dosage or alter drug treatment, attention to medication side effects/toxicity, management of comorbid conditions, and risk of polypharmacy. This course will review pathophysiology, clinical features, principles of diagnosis and treatment in relation to stage of PD, and other considerations important to optimal patient care.

BACKGROUND

The clinical syndrome known as parkinsonism was first described in 1817 by the English physician James Parkinson as "the shaking palsy" [5]. This disorder is characterized by the motor symptoms of resting tremor, muscle rigidity, and bradykinesia. Over time the non-motor features of PD have been increasingly identified, including sensory, autonomic, and neuropsychiatric symptoms, some of which appear before motor abnormalities are evident. Although the precise cause of PD is unclear, disease manifestations result from disruptions of dopaminergic neurotransmission within the central, peripheral, and autonomic nervous systems. The defining pathologic feature of PD is the loss of dopamine-producing cells and local deposition of aggregates of the protein alpha-synuclein (Lewy bodies) in the substantia nigra region of the brain [6].

Onset of PD is insidious, the course progressive, and neurologic signs are often asymmetrical. The four primary motor symptoms and signs are [6]:

- Tremors of the hands, arms, legs, and jaw
- Stiffness and rigidity of the limbs and trunk
- Bradykinesia (slowness of movement)
- Postural instability caused by impaired balance and coordination

As symptoms gradually become more pronounced, the simple tasks of daily living (e.g., walking, talking, swallowing) are increasingly difficult. Non-specific symptoms of PD include sleep behavior disorder, constipation, labile emotional state, and depression. While the symptoms are amenable to treatment, the disease eventually becomes disabling for most patients [6].

There is no blood test or other laboratory procedure proven to be specific for the diagnosis of PD [6]. The diagnosis rests on clinical findings and pattern of progression, often requiring multiple examinations over time. Laboratory testing and neuroimaging is useful to exclude other diagnostic possibilities. Drug treatment of PD is directed toward replenishing local tissue dopamine levels in order to facilitate neurotransmission and improve motor function. Effective long-term management is rendered best by an interprofessional team care approach.

DEFINITIONS

Parkinsonism: A motor disorder syndrome and core clinical feature of PD that includes bradykinesia plus tremor, rigidity, and/or postural instability. Parkinsonism is non-specific, as corticobasal degeneration, multisystem atrophy, and other neurodegenerative disorders may show features of parkinsonism. All patients with PD have parkinsonism, but not all patients with parkinsonism have PD [1; 7; 8].

Idiopathic Parkinson disease: Synonymous with PD, the most common cause of parkinsonism. Idiopathic means unknown cause, and idiopathic PD refers to parkinsonism not attributed to corticobasal degeneration, multisystem atrophy, or other neurologic disorder and not the direct result of gene mutation [1; 7; 8].

Sporadic Parkinson disease: PD without direct familial/genetic cause. Synonymous with idiopathic PD.

Bradykinesia: An abnormal degree of slowness when initiating voluntary movement and progressive reduction in speed and amplitude with repetitive movement. The core motor symptom of PD.

Dementia: The progressive decline in cognitive function due to neurologic damage or disease, with decline greater than expected from normal aging.

Dyskinesia: Involuntary movements with a rotatory, writhing appearance that can affect the limbs, trunk, or face. Dyskinesias are typically associated with dopaminergic therapy in later PD.

"On" and "off" states: With long-term levodopa use in later PD, many patients develop fluctuating drug response, termed "on" and "off" motor states. "On" describes optimal motor response to medication (typically levodopa); "on with dyskinesias" describes involuntary writhing movements during medication efficacy. "Off" describes resurgent motor symptoms and impairment, sometimes accompanied by non-motor symptoms such as low mood or fatigue. "Off" episodes commonly occur during loss of medication effect before the next dose [1; 7; 8].

EPIDEMIOLOGY

PREVALENCE AND INCIDENCE

Sporadic (idiopathic) PD is the second most frequent neurodegenerative disorder after Alzheimer disease [6]. The prevalence of diagnosed PD in the United States is estimated to be 500,000, but the Parkinson's Foundation Prevalence Project estimates the actual number is 930,000 [6; 9]. Approximately 60,000 new cases are diagnosed each year, the majority of which are people older than 60 years of age. The prevalence of PD increases with age in both men and women; it is 1% in persons 60 years of age or older and up to 4% in those older than 80 years of age. About 10% of patients with PD had onset of illness before 50 years of age. Women develop PD at a lower rate and with later onset than men; delayed onset has been attributed to neuroprotective

effects of estrogen on the nigrostriatal dopaminergic system [1; 2]. The direct cost of treating PD in the United States is estimated to be $14 billion annually, and the indirect costs add another $6.3 billion [6]. Because of increasing longevity, the prevalence of PD is predicted to exceed 1.2 million by 2030 and to double by 2040 [9].

DEMOGRAPHICS

The incidence of PD varies by age, race, and ethnicity. The ratio of men to women is roughly 2:1 [10]. As noted, the incidence is markedly higher in each decade after 60 years of age, peaking after 80 years of age. The rate is highest among Hispanic individuals, followed by non-Hispanic Whites, Asians, and Black persons [10]. However, there is some variation in the incidence in each racial/ethnic group when divided by sex, with Black men and Asian women at greater risk than their other-sex counterparts. The variable prevalence of PD throughout the world suggests that environmental and genetic factors interact with ethnic differences in disease pathogenesis [2].

MORTALITY RATES

The United States has the fourth highest annual death rate from PD in the world. In 2021, 38,536 people died from PD, the 15th most common cause of death in the United States. From 1999 to 2021, there was a 45% increase in the annual death rate from PD (from 5.4 to 9.8 per 100,000 persons) [11]. Between 2000 and 2021, age-adjusted death rates from PD per 100,000 increased for men (8.8 to 14.5) and women (3.9 to 6.6) [11].

RISK FACTORS AND ETIOLOGY

Idiopathic PD, like other neurodegenerative diseases, has a complex pathogenesis involving the interaction of several genetic contributions, each with minor impact, with environmental factors [12]. Risk factors associated with the development of PD include other medical conditions, abnormal physiologic processes, and exposure to specific substances and environmental toxins. Genetic associations are less robust, but several gene mutations confer greater risk of PD (***Table 1***).

RESEARCH

Current understanding of how environmental factors increase or mitigate risk of developing PD was accelerated by a series of studies from two distinct lines of investigation. These investigations identified specific protective and risk factors, greatly contributing to the knowledge of pathogenesis and pathophysiology in PD.

Identification of Factors Protective Against PD

The first line of investigation began in the early 1960s, with an unexpected finding that linked cigarette smoking with protection against PD. This association between smoking and neuroprotection from PD has been replicated in numerous epidemiologic, pre-clinical, and case-control studies. These studies also identified coffee drinking (and caffeine) as a factor that reduced risk of developing PD [13].

In these studies, risk of developing PD is shown as odds ratio (OR), where the odds of developing PD in cigarette or coffee users was compared to non-user reference groups. An OR of 1.00 signifies no difference from the reference group, while a number greater than 1 means increased odds of developing PD and a number less than 1 indicates decreased odds of PD.

In one study, smoking, other lifestyle behaviors, family history of PD, and their interaction were examined for possible association with risk of PD diagnosis by comparing 1,808 patients in Denmark with PD diagnosis with 1,876 matched population controls [14]. Strong inverse associations were found between cigarette smoking and risk of PD, even in smokers who quit 10 years before PD diagnosis. Compared with never-smokers without PD family history, the OR was 2.81 in never smokers with family history, versus 1.60 in smokers with family history. Duration had the greatest effect in modulating the smoking-PD relationship. Current smokers who smoked 40 years or more had ORs as low as 0.30. Unlike the correlation between longer smoking and lower PD odds, smoking more than 10 cigarettes per day did not further reduce odds.

RISK AND GENETIC FACTORS ASSOCIATED WITH PARKINSON DISEASE	
Category	**Risk Factors**
Medical conditions and lifestyle factors	Post-infection states Head trauma Elevated cholesterol High caloric intake
Substance use	Methcathinone (manganese content) Methamphetamine and amphetamines
Environmental toxins	Herbicides and pesticides Methanol and organic solvents Carbon disulfide Cyanide
Inflammatory, immune, and oxidative processes	Inflammation with microglia activation Mitochondrial dysfunction Nitric oxide toxicity Oxidative stress Signal-mediated apoptosis
Gene mutations	Alpha-synuclein gene (*SNCA*) Eukaryotic translation initiation factor 4 gamma 1 gene (*EIF4G1*) Glucocerebrosidase gene (*GBA*) Leucine-rich repeat kinase 2 (*LRRK2*) gene loci PTEN-induced putative kinase 1 (*PINK1*) gene loci Superoxide dismutase 2 gene (*SOD2*) Vacuolar protein sorting 35 homolog gene (*VPS35*)
Source: [1]	*Table 1*

Moderate coffee intake (3.1 to 5 cups per day) (vs. no coffee intake) showed an OR of 0.45. Moderate alcohol intake (3.1 to 7 units per week) (vs. no alcohol use) was associated with an OR of 0.60; higher daily alcohol did not further reduce the odds of developing PD. Stronger negative OR for PD was found in smokers with medium-high coffee or moderate alcohol intake than with each alone. Coffee intake association with lower PD odds was found in men and women; only men showed lower risk estimates with caffeine and alcohol, largely attributed to beer consumption [14].These findings were consistent with numerous prior studies, including publications from the prospective NIH-AARP Diet and Health Study [8; 15]. In this study, 306,895 participants (58.8% male, 50 to 71 years of age) were evaluated in 1995–1996 and again in 2000–2006 for development of PD.

One NIH-AARP study examined caffeine intake, risk of PD, and whether smoking affected this relationship [15]. Higher caffeine uses in 1995–1996 were associated with lower risk of PD diagnosis in 2000–2006 for men (OR=0.75) and women (OR=0.60). The linear trend for lower odds with higher caffeine was significant for both sexes [15].

The authors also performed a meta-analysis, which confirmed the inverse association between caffeine intake and risk for PD in men and women. Together with the study findings, this data led the researchers to conclude that gender differences do not influence caffeine risk reduction of PD. Smoking and caffeine may act independently to reduce PD risk [15].

Another NIH-AARP study examined cigarette smoking and risk of PD by comparing those who developed PD to those who did not. Odds for developing PD were 0.78 in past smokers and 0.56 in current smokers, with 0.47 in men and 0.74 in women.

For few current smokers at baseline who developed PD, other comparisons were not relevant [16]. The greatest reductions in odds for PD were found with current smoking and higher daily amount/duration of past smoking [16].

In the NIH-AARP study, amount and type of alcohol use was studied for risk of PD. Compared to non-drinkers, the odds ratio for developing PD was 0.73 with 1 to 1.99 drinks of beer per day, 1.22 with liquor, and 0.74 with wine. Beer and liquor consumption showed opposite effects [17].

Changes in smoking and alcohol consumption and combined changes in smoking and alcohol consumption frequencies and risk of PD were evaluated in one study that examined National Health Insurance Service (NHIS) data between January 2009 to December 2011 [18]. A total of 3,931,741 patients were included and followed up for incidence of PD until December 2017. Compared with sustained nonsmokers, sustained light, moderate, and heavy smokers had a lower risk of PD. Compared with sustained light drinkers, sustained light, moderate, and heavy drinkers showed decreased risk of PD [18]. Non-drinkers who began drinking to a light level were at decreased risk of PD. Non-smokers and non-drinkers who initiated smoking only, drinking only, and both smoking and drinking also showed decreased risk of PD [18].

Higher circulating levels of uric acid have also been associated with decreased incidence of PD and with slower rate of decline in patients with PD. This suggests a link to the neuroprotective effects of caffeine and the purinergic system [8; 19].

Identification of Environmental Risk Factors

A second line of investigation began when the first environmental risk factor was identified. In the early 1980s, a parkinsonism syndrome developed in persons who used a tainted street drug. An illicit lab produced a meperidine (Demerol) analog that contained 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), a neurotoxic impurity. MPTP crosses the blood-brain barrier and is oxidized to 1-methyl-4-phenylpyridinium (MPP+) by monoamine oxidase (MAO)-B. MPP+ is a neurotoxin that, following dopamine neuron uptake via the dopamine transporter, destroys striatal dopamine neurons by inhibiting mitochondrial complex I activity. Ten persons who ingested this batch developed a severe, irreversible parkinsonism syndrome [20; 21]. Extensive evaluation of these patients at onset and over time led to many breakthroughs in the understanding of PD and related conditions. Also identified were several persons with MPP+ exposure who developed mild-to-moderate, but not severe, parkinsonism. For the first time, an environmental factor was linked to PD pathogenesis, initiating environmental risk factor research. The variable consequences from exposure also helped prompt research into protective factors [20; 22; 23; 24].

ENVIRONMENTAL RISK FACTORS

Paraquat and rotenone are two pesticides (i.e., herbicides, insecticides, fungicides, and rodenticides) known to increase the risk of developing PD. Neurotoxic mechanisms have been proposed based on findings that substances such as MPTP cause selective damage to dopaminergic neurons in the nigrostriatal pathway through mitochondrial complex I toxicity [8].

Paraquat exposure induces reactive oxygen species formation; while not shown to stimulate Lewy body formation, this does accelerate alpha-synuclein misfolding, disrupt membrane conductance, and accelerate protein aggregation [25; 26]. Rotenone inhibits mitochondrial complex I, enhances alpha-synuclein fibril formation, and increases alpha-synuclein aggregation, modification, misfolding, and toxicity [27; 28]. The data suggest environmental factors that increase oxidative stress or inhibit mitochondrial function can lead to alpha-synuclein misfolding and nigrostriatal damage, processes that underlie PD [8].

A Utah retrospective study of methamphetamine or amphetamine use as a risk factor for PD/parkinsonism/essential tremor was performed by examining statewide medical records (1996 through 2011) of people 30 years of age and older. A methamphetamine/amphetamine cohort and cocaine cohort were compared to a population control cohort

unexposed to drugs or alcohol. Methamphetamine/amphetamine users showed increased risk compared to population controls; cocaine users did not exhibit elevated risk of PD compared to controls. The three-fold increased risk of PD in methamphetamine/amphetamine users confirmed prior observations and suggests PD risk in users may be higher than previous estimates. A suggestion that female and male users may differ in PD susceptibility warrants further study [29].

Pre-clinical research identified nicotine exposure as a possible protective factor against methamphetamine-induced dopaminergic deficits [30]. Using oral nicotine exposure as the measure, researchers found that regular nicotine exposure from adolescence through mid-adulthood attenuated methamphetamine-induced striatal dopaminergic deficits associated with this drug use in early adulthood. High-dose nicotine attenuated the negative effects of methamphetamine in late adolescence, but the protective effects did not persist. High-dose nicotine exposure from late adolescence through early adulthood did not protect against methamphetamine in early adulthood, but high-dose nicotine from post-adolescence to full adulthood did protect against methamphetamine in mid-adulthood.

Nicotine neuroprotection is not from an alteration of methamphetamine pharmacokinetics; it derives from the effects on nicotinic acetylcholine receptors (nAChRs). Studies show that nicotine increases striatal α4β2 nAChR expression, while methamphetamine and nicotine decrease striatal α6β2 nAChR expression. This suggests that nicotine protects against methamphetamine-induced striatal dopaminergic deficits by affecting α4β2 and/or α6β2 expression, with additional influence from nicotine exposure duration and the age of onset [30].

A meta-analysis of data from this study concluded that higher body mass index (BMI) in overweight (BMI 25–29.9) or obese (BMI ≥30) persons had no impact on the risk of developing PD [31].

GENETIC RISK FACTORS

Inherited genetic mutations are responsible for a small proportion of PD, with the most common genetic form of PD, *PARK8*, accounting for 2% of PD cases in the United States [32]. Penetrance is incomplete in this inherited parkinsonism, and PD manifestation in carriers is determined by environmental exposure or other genetic factors [32].

Idiopathic PD is a sporadic disorder, and twin studies have not shown a strong genetic basis in patients older than 50 years of age. However, genetic mutations have been increasingly mapped, and rare autosomal dominant and recessive familial forms have been identified in small numbers of patients. These include the *SNCA, Parkin, PINK-1, DJ-1,* GBA, and *LRRK2* genes that code various proteins, with some carrying the same name as the mutation and components of the ubiquitin-protease system. In addition, mutations in the gene encoding glucocerebrosidase, the enzyme deficient in Gaucher disease, confer a greater risk of PD [33; 34].

The protein alpha-synuclein is a key element in Lewy pathology and contributes to familial and sporadic PD. Duplications and triplications of wild-type *SNCA*, the gene encoding alpha-synuclein, have been identified in typical and early-onset PD, suggesting *SNCA* overexpression is related to PD pathogenesis [8].

RISK FACTOR INTERACTIONS

Gene-environment interactions in PD were examined by studying smoking and caffeine use interaction with 10 single nucleotide polymorphisms at or near four PD susceptibility genes in 584 patients with PD and 1,571 controls. Combining smoking and caffeine exposure showed significant interaction with one single nucleotide polymorphism at *SLC2A13*, near *LRRK2*. Each A allele was associated with a 35% increase in PD risk in never-smokers with low caffeine intake and a 32% lower risk in smokers with high caffeine intake. This study suggests a potential gene-environment interaction for PD [35]. One study of 4,488 Asian participants found that caffeine intake interacts with *LRRK2* risk variants across three different groups of gene

carriers. Asymptomatic risk-variant-carriers who did not drink caffeine were found to have four to eight times greater risk of PD compared with wildtype carriers/caffeine drinkers [36].

History of traumatic brain injury also increases PD risk [37]. The *SNCA* Rep1 variation may mediate the association between brain injury and PD risk. Pooled results from two case-control studies found head injury unrelated to risk of later PD, but relative to subjects with medium-length Rep1 alleles, head injury was strongly associated with PD in those with long Rep1 alleles. Those with both head injury and long Rep1 were diagnosed with PD an average of five years before those with neither risk factor. High levels of alpha-synuclein (as with Rep1 expansion) may initiate and/or accelerate neurodegeneration following head injury [38].

PATHOPHYSIOLOGY

Unless otherwise stated, the following discussion pertains to sporadic (idiopathic) PD (i.e., cases lacking heritable/gene mutation cause).

DOPAMINERGIC PATHOPHYSIOLOGY AND LOSS OF MOTOR FUNCTION

PD is the most common form of neurodegenerative parkinsonism, a syndrome characterized by progressive deterioration in motor abilities resulting from dopaminergic neuron loss in the substantia nigra pars compacta and ventral tegmental area. Dopamine neuron loss is most prominent in the ventral lateral substantia nigra; 60% to 80% of these neurons are lost when motor symptoms emerge and PD is diagnosed [6; 12].

Substantia nigra pars compacta dopamine neuron loss and striatal dopaminergic deficits, including nicotinic receptor-mediated dopaminergic signaling, underlie motor symptom development in PD. The results of numerous studies linking cigarette smoking with protection against PD are explained by the actions of nicotine. Acetylcholine influences striatal dopamine release predominantly through action at nAChRs, and nicotine protects against nigrostriatal damage by stimulating nAChRs. Modulation of the nicotinic cholinergic system is an active area of PD research, also fueled by evidence that nAChR drugs may reduce PD progression and levodopa-induced dyskinesias [13; 39].

Structural and Functional Pathophysiology

The origin of motor dysregulation in PD is neuronal degeneration in the substantia nigra pars compacta and loss of dopaminergic regulation of the striatum. The striatum is an entry point for cortical projections into the basal ganglia. The basal ganglia-thalamocortical motor circuit modulates the cortical output required for normal movement. Cortical signaling enters the striatum and is processed through the basal motor circuit; motor circuit output is relayed through the internal globus pallidus and the substantia nigra pars reticulata. The basal ganglia circuit involves two dopaminergic pathways:

- The direct pathway of striatal neurons with dopamine D1 receptors, projecting to the globus pallidus and substantia nigra reticulata
- The indirect pathway of striatal neurons with D2 receptors, projecting to the striatum/external globus pallidus connection and the external globus pallidus/subthalamic nucleus connection

In PD, striatal dopamine depletion deactivates the excitatory D1 direct pathway and hyperactivates the inhibitory D2 indirect pathway. Alterations in these two pathways inhibit voluntary movement [6; 8; 12].

Pathogenic Mechanisms

There is a consistent line of evidence linking PD to a neurodegenerative process involving oxidative stress, mitochondrial dysfunction, and neuroinflammation. Environmental and genetic factors induce mitochondrial dysfunction, resulting in abnormal accumulation of miscoded proteins (mostly alpha-synuclein) and generation of oxidative stress in enteric, peripheral, and central nervous systems. In turn, oxidative stress, excitotoxicity, and mitochondrial dysfunction promote the destruction of dopamine neurons and dopaminergic function in midbrain systems [12; 40; 41; 42].

CORE PATHOLOGIC FEATURES

Along with substantia nigra dopamine neuron loss, postmortem confirmation of PD diagnosis requires the presence of Lewy body pathology—intraneuronal aggregates of misfolded (pathogenic) forms of the protein alpha-synuclein. In addition to other pathologic effects, alpha-synuclein aggregates are associated with axonal and neuronal dysfunction, sequestration of vital neurotransmitter enzymes, and reduction or loss of cytoplasmic tyrosine hydroxylase and choline acetyltransferase. These effects compromise cellular integrity and fuel degeneration and contribute to neuronal death [43].

A third pathologic feature of PD is increased gliosis. Gliosis refers to an increased number and activation state of astrocytes and microglia, glial cell types that respond to injury or damage with altered morphology and production of inflammatory molecules. Increased gliosis is found in areas of neurodegeneration, which is not limited to the nigrostriatal pathway but evident throughout the brain to suggest a generalized neuroinflammation. Misfolded alpha-synuclein aggregates directly activate microglia, further linking alpha-synuclein and neuroinflammation to PD. These findings support a role of the innate immune system in the neurodegenerative process of PD [8].

DEVELOPMENT AND PROGRESSION OF PATHOPHYSIOLOGY

Neuroscience findings have transformed the concept of PD, now recognized as a disease with pathology distributed throughout the enteric, peripheral, and central nervous systems. Nigrostriatal motor pathology is one pathophysiologic phase on a continuum of processes that begin long before motor symptoms emerge [8; 12; 44].

An essential initiating event for PD is induction of alpha-synuclein misfolding. This is followed by aggregation of misfolded alpha-synuclein and initial formation of alpha-synuclein aggregates in neurons. Very few neuron types are vulnerable to alpha-synuclein inclusions; the most vulnerable are projection neurons with long, thin, sparsely myelinated axons. Glutamatergic, gamma aminobutyric acid-ergic, dopaminergic, noradrenergic, serotonergic, histaminergic, and cholinergic projection cells can become involved, but within neurotransmitter types, some subgroups are selectively vulnerable (dopaminergic substantia nigra pars compacta neurons) while others are not (dopaminergic hypothalamic neurons) [45].

Neurons with the greatest exposure to potentially hostile environmental factors are selectively vulnerable to alpha-synuclein inclusions. Aggregates form in these enteric, peripheral, and central neurons and propagate trans-synaptically from neuron to neuron. A regional distribution pattern of aggregated alpha-synuclein emerges through specific involvement of susceptible and axonally interconnected projection neurons within the nervous system [43; 46].

Evidence indicates that PD originates in structures outside the brain, including the enteric nervous system of the gastrointestinal tract and salivary glands. The olfactory bulb has very early involvement. A primary route of disease progression is through enteric nervous system neuronal connections to the vagal nerve nucleus in the lower brainstem. The pathology then spreads through visceromotor and somatomotor brainstem centers to the locus coeruleus, basal forebrain, striatum, basal ganglia-thalamocortical motor circuit, central amygdala, and cortical structures. Other routes are through spinal cord centers via descending projections from lower brainstem nuclei and from autonomic projections connecting the enteric nervous system with spinal cord peripheral ganglia and preganglionic nuclei [6; 8; 43].

A classification method was developed to identify the extent of postmortem pathology resulting from PD. This system uses six stages to roughly demarcate the sequence of anatomic involvement and symptom emergence throughout the disease course (***Table 2***). The stages occur in two phases: the preclinical phase (stages 1 through 3) and the clinical, or motor, phase (stages 4 through 6). Each stage includes newly affected regions along with those involved in previous stages [6; 43; 44; 47; 48].

STAGES OF PARKINSON DISEASE	
Stage	**Description**
Preclinical phase	
1	Lesions (Lewy body pathology/alpha-synuclein aggregates) develop in olfactory structures, salivary glands, enteric and peripheral autonomic nervous system, parasympathetic and sympathetic ganglion projection neurons, and lamina I of the spinal cord.
2	The pathologic process enters the lower brainstem, including vagal nerve projection neurons that connect the enteric nervous system with the central nervous system, the lower raphe nuclei, and the locus coeruleus.
3	Lesions spread in the midbrain tegmentum, the basal forebrain, and into the substantia nigra.
Clinical (motor) phase	
4	The pathology is entrenched in the substantia nigra pars compacta and infiltrates the amygdala, the intralaminar thalamic nuclei, and the hippocampal CA2 sector.
5	Lesions spread in the cingulate and temporal cortex.
6	Lesions infiltrate the frontal and parietal cortex.
Source: [6; 43; 44; 47; 48]	*Table 2*

PD is clinically diagnosed by the presence of cardinal motor features, broadly defined as bradykinesia, rest tremor, rigidity, and postural/gait impairment. The inclusion of postural/gait dysfunction in clinical criteria has been challenged, because it typically appears later in the disease course (instead of during the onset of motor symptoms) and is influenced by non-dopaminergic pathology primarily involving cortical cholinergic neurodegeneration [49]. Some research is focused on development of a biologic staging system of PD [50; 51].

NATURAL HISTORY OF DISEASE PROGRESSION

The progression of disease and disability in PD varies and is partially influenced by patient factors such as age. In general, from the mean age at diagnosis of 61 years, the mean time to death is 14 years overall. Survival time is a mean 24 years for patients diagnosed in their 40s and 9.7 years for patients diagnosed in their 70s [4]. With the onset of subclinical non-motor symptoms decades before diagnosis, pathologic processes that underlie PD are probably active over a 40-year period in many patients [48].

Throughout the disease course, all patients experience deterioration in motor function associated with increased impairment and disability and declining quality of life. The later stages of the disease are characterized by reduced efficacy of oral medication, increased medication-related side effects, dysphagia, cognitive dysfunction with conversion of mild cognitive impairment to dementia, reduced mobility with increased tendency to fall, and in many, dependence on others for activities of daily living. The mode of death often involves respiratory compromise from bronchopneumonia or aspiration [4].

Mild cognitive impairment later progressing to dementia is very prevalent in patients with PD; roughly 80% of patients develop dementia within 20 years of diagnosis. Cerebrospinal fluid levels of alpha-synuclein predict the progression of cognitive decline in PD [52]. Dementia in PD and Alzheimer disease is associated with central nervous system (CNS) accumulation of protein aggregates such as b-amyloid peptide. B-amyloid peptide deposition in the striatum strongly correlates with dementia, suggesting this accumulation is a contributing factor to the development of cognitive impairment and neurodegeneration in PD [53]. Subjects with PD and

dementia show degeneration of several subcortical nuclei, including the cholinergic nucleus basalis of Meynert, the medial substancia nigra, and the noradrenergic locus coeruleus. Presence of secondary neuropathologies may further increase oxidative stress, decrease brain energy, and enhance brain degenerative processes in patients with PD [12].

NON-MOTOR SYMPTOM APPEARANCE AND DISEASE STAGE

PD is typically diagnosed following the onset of motor features (stage 4) that prompts the patient to seek medical attention. Pre-motor prodromal disease can manifest in non-motor features, such as depression, fatigue, rapid eye movement (REM) sleep behavior disorder, anosmia, and constipation, that reflect disease involvement in autonomic, enteric, or somatomotor systems. Visuospatial and cognitive dysfunction, especially mild cognitive impairment with dominant executive dysfunction manifested in diminished multitasking, planning, retrieval, concentration, and attention performance, are increasingly recognized as prevalent in earlier stages [4]. As mentioned, physical appearance, severity, and progression of pre-motor and motor features corresponds to the nervous system and brain areas afflicted by pathologic infiltration [47; 54; 55; 56].

Motor symptoms can also appear long before diagnosis. A prospective study found motor symptom onset 10 years before formal PD diagnosis. In this study, primary care patients were assessed for prodromal PD symptoms at three time points over 10 years. Symptom frequency was compared in patients later diagnosed with PD with those remaining PD-free (controls). Some symptoms were not analyzed [54]. Ten years pre-diagnosis, tremor was 7.6 times more likely and constipation twice as likely in patients who developed PD than in controls. Five years pre-diagnosis, patients who developed PD were more likely to show tremor, balance impairments, constipation, hypotension, erectile dysfunction, urinary dysfunction, dizziness, fatigue, depression, and anxiety than controls.

The progression of non-motor symptoms in PD, and stage of pathophysiologic progression that underlies their emergence, is shown in ***Table 3*** [8; 44; 57].

It should be noted that PD is heterogeneous, and not all patients exhibit full-blown motor and non-motor syndromes. Some patients exhibit motor features that remain modest in severity for many years, or cognitive and behavioral functions that appear normal or minimally affected. Overall, the clinical features are most easily viewed as motor and non-motor components of the PD phenotype [8].

PRE-MOTOR SYMPTOMS

Several pre-motor symptoms have been studied for their relationship to disease process and PD diagnosis.

REM Sleep Behavior Disorder

REM sleep behavior disorder is characterized by dream enactment behavior during sleep, including yelling, laughing, or crying; complex voluntary movements; falling out of bed; and even violent behaviors with injury. REM sleep behavior disorder is an extremely powerful predictor, or prodromal marker, of developing synuclein-mediated neurodegenerative diseases, which eventually occurs in at least 80% and most frequently involves PD [58; 59].

A 16-year follow-up study of men diagnosed with REM sleep behavior disorder found that 80.8% eventually developed parkinsonism/dementia and were diagnosed with PD (62%); dementia with Lewy bodies (14%); multisystem atrophy (9.5%); clinically diagnosed, autopsy-confirmed Alzheimer disease plus Lewy body pathology (9.5%); or profound unspecified dementia (5%) [60]. Of those who progressed to parkinsonism, the mean age of REM sleep behavior disorder onset was 57.7 years; the mean age of parkinsonism/dementia onset was 71.9 years. Overall, the mean interval from REM sleep behavior disorder onset to parkinsonism/dementia onset was 14.2 years (range: 5 to 29 years). In these patients, lower brainstem involvement, particularly the pons, appeared long before the onset of motor features [60].

PATHOLOGY AND NON-MOTOR SYMPTOMS IN VARIOUS STAGES OF PARKINSON DISEASE			
Non-Motor Symptoms	**Stage**	**Symptoms/Signs**	**Affected Nervous System Areas**
Sensory			
Olfaction	1	Decreased odor detection, identification (hyposmia)	Olfactory bulb Anterior olfactory nucleus
Pain	2, 3	Vague discomfort Burning pain or paresthesia	Serotonergic pathways Dopaminergic pathways
Autonomic			
Gastrointestinal	1	Nausea Constipation Decreased gastric emptying Colonic dysmotility Esophageal dysmotility	Dorsal motor nucleus of the vagus Enteric ganglia
Genitourinary	2	Urinary frequency, urgency Incontinence Erectile dysfunction	Gain setting neurons Pelvic autonomic ganglia
Cardiovascular	1	Orthostatic hypotension	Dorsal motor nucleus of the vagus Sympathetic ganglia
Thermoregulatory	3, 4	Hyperhydrosis Hypohydrosis/anhydrosis	Sympathetic ganglia Hypothalamus
Neuropsychiatric			
Sleep disorders	2, 3	Sleep cycle disruption Excessive daytime sleeping REM sleep behavior disorder	Locus ceruleus/subceruleus Raphe nuclei Pedunculopontine nucleus Suprachiasmatic nucleus
Behavioral disorders	2, 3	Apathy Depression Anxiety	Locus ceruleus Raphe nuclei Ventral tegmental area
Dementia	4, 5, 6	Bradyphrenia Executive dysfunction Memory decline Visuospatial impairment	Dopaminergic (substantia nigra, ventral tegmental area) Cholinergic (nucleus basalis of Meynert) Cortical/subcortical pathology
Source: [8; 44; 57]			*Table 3*

The first published methodology with high accuracy in predicting PD development used data from patients with REM sleep behavior disorder. These patients were regularly evaluated throughout the 10-year period following their initial REM sleep behavior disorder diagnosis. Using this data, prodromal markers of PD were analyzed for predictive validity. Factors that highly predicted PD when combined were (in descending order of strength) subtle motor dysfunction, nonuse of antidepressants, abnormal color vision, olfactory loss, and advanced age. Factors found non-predictive when aggregated were mild cognitive impairment, depression, "Parkinson personality," treatment with clonazepam or melatonin (for REM sleep behavior disorder), autonomic markers, and male sex [58].

Olfactory Dysfunction

Studies of olfaction in PD have shown abnormalities in up to 100% of patients, making olfactory dysfunction the most robust predictor of developing PD. As noted, many patients complain of declining sense of smell long before parkinsonism onset. As it is not disabling and relatively nonspecific, anosmia has mostly failed to gain traction as a predictive and clinical feature of PD [61].

Constipation

Constipation is a notoriously bothersome and common symptom in PD that results from peripheral autonomic involvement in the early pathogenic process [61]. Compared with middle-aged men who reported more than two bowel movements per day, men who reported fewer than one bowel movement per day were prospectively identified as more than four times more likely to develop PD. This suggests lower bowel involvement is an early sign that, in some patients, predated PD by 15 years or more [62].

Excessive Daytime Sleepiness

Excessive daytime sleepiness has also been identified as a midlife risk factor for PD, suggesting early brainstem involvement and subsequent sleep disturbances as a pre-diagnostic feature [63].

ASSESSMENT AND DIAGNOSIS OF PARKINSON DISEASE

As noted, parkinsonism refers to the motor features of bradykinesia, tremor, rigidity, and postural instability resulting from nigrostriatal dopamine neuron loss in PD, as well as dementia with Lewy bodies, multisystem atrophy, progressive supranuclear palsy, and corticobasal degeneration. PD is the most common cause of parkinsonism, comprising 80% of cases [64].

The centrality of the motor syndrome remains the core feature that defines clinical PD and by which PD is diagnosed. However, the pathologic process of PD is now established as beginning in non-dopaminergic structures of the brain or peripheral nervous system, during which non-motor features dominate. This is reflected in a new diagnostic classification scheme that recognizes prodromal PD as a true stage of PD, and in the 2015 International Parkinson and Movement Disorder Society (MDS) PD diagnostic criteria that incorporate non-motor manifestations of PD [65].

Non-motor symptoms of PD appear before motor symptoms and are usually present at diagnosis or develop and progress in severity throughout the disease course. Non-motor symptoms may appear as early as three decades before motor features, during the prodromal PD phase. They develop earlier in the neurodegenerative process than motor features, which require 60% to 80% loss of dopaminergic neurons to emerge [44]. Criteria for prodromal PD have been published, and while early detection of PD before the onset of motor features could be immensely valuable, the absence of neuroprotective or disease-modifying therapy against PD, ethical issues from disclosure of disease risk, and the frequently shifting understanding of PD discourage any attempts to clinically diagnose the motor symptom prodrome of PD [66]. Nonetheless, identification and treatment of non-motor symptoms are essential due to their potentially great negative impact on patient well-being [1; 6].

CLINICAL FEATURES

Motor Symptoms of PD

In PD, the cardinal motor features of bradykinesia, resting tremor, rigidity, and postural/gait impairment reflect parkinsonism [67]. A mnemonic for the core motor features is TRAP [8]:

- **T**remor at rest
- **R**igidity
- **A**kinesia (i.e., bradykinesia and hypokinesia)
- **P**ostural instability

It is important to note that postural instability, while a cardinal motor feature, is seldom a problem early in the course of PD and may not be evident at diagnosis, as it usually appears later in the disease course [65].

Bradykinesia

Bradykinesia, as typically defined, combines the definitions of bradykinesia (slowness) and hypokinesia (decreased movement amplitude) [65]. Bradykinesia is reduced speed in initiating and executing movement, and altered fine motor control and dexterity.

It is not just slowness in movements, but slowness in initiating voluntary movement, with progressive fatiguing during repetitive movements that presents in reduced speed and amplitude during finger or foot tapping. Slowness of movements, progressive reduction in speed and amplitude of repeated movements, delay in initiating movements, and freezing gait eventually occur in 80% to 90% of patients with PD [68].

Bradykinesia is the defining feature of parkinsonism and the essential clinical sign because the slowed, disordered motor movements directly correlate with functional abnormality in basal ganglia-cortical neuronal circuits, where aberrant dopamine-mediated firing patterns within indirect and direct pathways inhibit activity in cortical motor system neurons [4; 8]. The slowed, small-amplitude movements in bradykinesia interfere with limb control, dexterity in tying shoes or buttoning shirts, and swallowing (dysphagia). It may also present as decreased facial expression and eye blinking (hypomimia), weak voice (hypophonia), and progressively smaller handwriting (micrographia) [4; 67; 69].

Rigidity

Rigidity is increased muscle tone in flexor and extensor muscle groups at rest and resistance to passive stretch movement in flexor and extensor muscles with the limb relaxed. Rigidity is present in 80% to 90% of patients with PD, usually unilaterally at the onset of motor symptoms. It often, but not always, co-occurs with tremor. Rigidity results from altered firing rates in the basal ganglia, a fundamental feature of parkinsonism. The resultant motor system output reflects inappropriate activation of agonist and antagonist muscles that present in bradykinesia and rigidity [8]. In early-stage disease, rigidity may manifest as pain, such as frozen shoulder or low back pain, obscuring the diagnosis of a CNS disorder [4].

Rest Tremor

Rest tremor, an initial symptom in 70% to 90% of patients, refers to a 4–6 Hz tremor in the fully resting limb, suppressed during movement initiation. Rest tremor is a rhythmic, oscillatory involuntary movement and one of the most characteristic signs in clinical medicine. The most distinguishing rest tremor is the "pill-rolling" type, with rubbing movements of thumb and index fingers against each other. Rest tremor is thought to initiate with nigrostriatal degeneration and subthalamic nucleus or globus pallidus disinhibition, or disrupted thalamo-cortical-cerebellar circuits leading to abnormal thalamic pacemaker cell function [4; 8].

Tremor in parkinsonism is distinct from other forms of tremor by its asymmetry, speed, dominance at rest, reduction or cessation during action, re-emergence when maintaining a posture, and increased amplitude during tasks requiring mental concentration [4].

Postural Instability

Postural instability is defined as difficulty adjusting to postural change, and together with gait impairment and postural abnormalities, it comprises the axial motor signs of PD [70]. Postural instability and other axial signs do not usually present in early PD, reflecting pathophysiology beyond dopamine motor neuron loss [8]. As such, the inclusion of axial signals in the cardinal motor features required for the parkinsonism diagnosis in PD has been challenged [65].

Postural and gait impairment result from loss of postural reflexes, which leads patients to adopt a stooped posture. The loss of postural reflexes is also a major contributor to falls [71]. In PD, the gait is slow, with short shuffling steps on a narrow base that appears as if the patient is chasing his or her own center of gravity. Patients show decreased arm swing; turning around is slow, with multiple small steps, and freezing gait can occur, especially in crowded or narrow places. Festination, a very fast succession of steps with the patient only able to stop when meeting an obstacle, may also be present. Walking and turning becomes difficult or impossible in patients with PD when additional cognitive load, such as dual tasking, is imposed [72; 73].

NON-MOTOR SYMPTOMS IN PARKINSON DISEASE	
Category	**Symptoms**
Autonomic dysfunction	Constipation Orthostatic hypotension Sexual dysfunction Sweating Urinary retention and urgency Sialorrhea (also from decreased swallowing movements)
Neuropsychiatric	Apathy Anxiety, panic attacks Cognitive deterioration, from mild impairment to dementia Depression (dysphoria, suicidal ideation) Impulse-control disorders (e.g., obsessions, hypersexuality, compulsive shopping, binge eating), usually associated with dopamine agonist use Psychoses (hallucinations, delusions)
Sensory symptoms	Olfactory dysfunction (hyposmia) Paresthesias (tingling, numbness), other abnormal sensations Decreased visual contrast and color discrimination Decreased visual motion perception
Sleep disturbance	Daytime somnolence Insomnia REM sleep behavior disorder Restless legs syndrome Sleep attacks Sleep apnea
Other	Fatigue Pain Weight loss
Source: [1; 4]	*Table 4*

Brainstem pathology is now recognized as a major contributor to the clinical features in PD. Postural control problems with imbalance, falls, and freezing gait tend to occur later in PD and reflect cholinergic neuron degeneration and dysfunction outside of the basal ganglia [8]. Persons with parkinsonism or other extrapyramidal neurodegenerative disorders frequently develop problems with balance and may experience frequent falls. The vestibular system controls balance and is synaptically linked to the extrapyramidal system, possibly contributing to posture and balance dysfunction [67].

Non-Motor Symptoms

The frequency and diversity of non-motor symptoms in PD is substantial, and includes autonomic, neuropsychiatric, olfactory, sensory, and sleep disorders that occur in 80% to 90% of patients (***Table 4***). Non-motor symptoms can manifest before, during, or after motor symptoms and may result in greater impairment of quality of life. The prevalence of cognitive, autonomic, and mood disorders is very high; progression can result in patients requiring care in a supervised environment [8].

A 2010 survey found that up to 62% of patients with PD do not volunteer symptoms such as apathy, pain, sexual dysfunction, bowel incontinence, constipation, or sleep disorders either through embarrassment or unawareness of symptom relevance to PD. Clinicians may not understand that these symptoms require assessment. Their under-reporting has important therapeutic and societal implications, as most are treatable. Left unaddressed, non-motor symptoms detrimentally affect patient quality of life, frequently lead to hospitalization and institutionalization, and quadruple the cost of PD care [74].

DIAGNOSTIC WORKUP

Disease-specific screening tests or biomarkers for PD are not yet available, and definitive diagnosis is only possible at autopsy by confirmation of striatal dopamine neuron loss and Lewy body pathology [69]. Idiopathic PD is diagnosed through patient history and physical examination, often performed sequentially over time in order to identify signs of progression and the emergence of defining clinical features. History or physical findings inconsistent with features of idiopathic PD are explored further to rule out or confirm an alternate diagnosis. Clinicians with limited experience caring for patients with PD should consider referring a patient with suspected disease to a physician with expertise in movement disorders to confirm diagnosis [2].

DIAGNOSTIC CRITERIA

The UK Parkinson's Disease Society Brain Bank Clinical Diagnostic Criteria have been the most widely used diagnostic criteria for PD, recommended for use in North America and Europe as a straightforward, objective, and accurate approach (***Table 5***) [4; 68; 75]. With these criteria, three major steps are required for PD diagnosis. The presence of parkinsonism must be established; however, parkinsonism is non-specific for PD, and additional steps are required for a PD diagnosis.

According to the European Academy of Neurology and the Movement Disorders Society European Section, only the Brain Bank clinical diagnostic criteria for Parkinson disease have been validated and are therefore recommended as probably effective for clinical practice.

(https://www.movementdisorders.org/MDS-Files1/MDS-ES/MDS-ES-EFNS/BerardellietalEFNSMDSESene12022.pdf. Last accessed April 28, 2025.)

Level of Evidence: B (At least one convincing prospective study or overwhelming evidence from retrospective studies)

The UK Brain Bank diagnostic criteria were established more than 30 years ago (in 1992) and solely address motor symptoms, leading many to consider them outdated. This led to the 2015 publication of new PD diagnostic criteria by the MDS Task Force, comprised of North American and European experts. These criteria better reflect current understanding of PD as a multi-system disorder affecting all parts of the nervous system, often with a genetic component and a very slow progression of neurodegenerative processes reflected in a long prodromal period. These aspects are incorporated in the new criteria [65].

The first essential criterion of the MDS Clinical Diagnostic Criteria for PD is parkinsonism, defined as bradykinesia with rest tremor and/or rigidity [65]. Examination of cardinal motor features should follow as described in the MDS-United Parkinson Disease Rating Scale (UPDRS) [76]. After parkinsonism is diagnosed, PD may be diagnosed as either clinically probable or established based on the presence or absence of absolute exclusion criteria, supportive criteria, and guideline-defined "red flags" (***Table 6***) [65]. Clinically probable PD diagnosis requires [65]:

- Absence of absolute exclusion criteria
- Presence of no more than two red flags counterbalanced by supportive criteria
- If one red flag is present, there must also be at least one supportive criterion
- If two red flags, at least two supportive criteria are needed

UK BRAIN BANK CLINICAL DIAGNOSTIC CRITERIA FOR PARKINSON DISEASE	
Step	**Criteria**
Step 1: Diagnosis of parkinsonian syndrome	Bradykinesia and one or more of the following: • Muscular rigidity • Resting tremor 4–6 Hz • Postural instability (not due to primary visual, vestibular, cerebellar, or proprioceptive dysfunction)
Step 2: Exclusion criteria for Parkinson disease	History of repeated strokes with stepwise progression of parkinsonian features History of repeated head injury History of definite encephalitis Oculogyric crises Neuroleptic treatment at onset of symptoms More than one affected relative Sustained remission Strictly unilateral features after three years Supranuclear gaze palsy Cerebellar signs Early severe autonomic involvement Early severe dementia with disturbances of memory, language, and praxis Babinski sign Cerebral tumor or communicating hydrocephalus on computed tomography scan Negative response to large-dose levodopa MPTP exposure
Step 3: Supportive positive criteria of Parkinson disease[a]	Unilateral onset Rest tremor present Progressive disorder Persistent asymmetry affecting side of onset most Excellent levodopa response (70% to 100% symptom reduction) Severe levodopa-induced chorea Levodopa response ≥5 years Clinical course ≥10 years
[a]Three or more required for diagnosis of definite PD.	
Source: [75]	*Table 5*

A diagnosis of clinically established PD is made if the patient displays [65]:

- Absence of absolute exclusion criteria
- At least two supportive criteria
- No red flags

The MDS PD criteria note that the establishment of parkinsonism motor features remains the foundation of PD diagnosis, but several pre-motor features are woven into the overall criteria [65]. While postural instability is a feature of parkinsonism, it is not a criterion for parkinsonism in the MDS guideline. Dementia with Lewy bodies is not considered an alternative parkinsonian syndrome; these patients can be diagnosed as PD (dementia with Lewy bodies subtype).

PATIENT HISTORY

Idiopathic PD is diagnosed by history and physical examination. The first step in the diagnostic process is taking a careful history by thoroughly questioning the patient and/or family members regarding [1; 4; 67]:

MDS CLINICAL DIAGNOSTIC CRITERIA FOR PD	
Absolute exclusion criteria	Unequivocal cerebellar abnormalities, such as cerebellar gait, limb ataxia, or cerebellar oculomotor abnormalities (e.g., sustained gaze evoked nystagmus, macro square wave jerks, hypermetric saccades) Downward vertical supranuclear gaze palsy, or selective slowing of downward vertical saccades Diagnosis of probable behavioral variant frontotemporal dementia or primary progressive aphasia within the first five years of disease Parkinsonian features restricted to the lower limbs for more than three years Treatment with a dopamine receptor blocker or dopamine-depleting agent in a dose and time-course consistent with drug-induced parkinsonism Absence of observable response to high-dose levodopa despite at least moderate disease severity Unequivocal cortical sensory loss (i.e., graphesthesia, stereognosis with intact primary sensory modalities), clear limb ideomotor apraxia, or progressive aphasia Normal functional neuroimaging of the presynaptic dopaminergic system[a] Documentation of an alternative condition known to produce parkinsonism and plausibly connected to the patient's symptoms, or the expert evaluating physician, based on the full diagnostic assessment, feels that an alternative syndrome is more likely than PD
Supportive criteria	Clear, dramatic benefit to dopaminergic therapy. During initial treatment, patient returned to normal or near-normal level of function. In the absence of documented initial response, dramatic response can be classified as: • Marked improvement with dose increases or marked worsening with dose decreases. Mild changes do not qualify. Document objectively (>30% change in MDS-UPDRS) or subjectively (clearly documented history of marked changes from a reliable patient or caregiver) • Unequivocal and marked on/off fluctuations, which must have at some point included predictable end-of-dose wearing off Presence of levodopa-induced dyskinesia Rest tremor of a limb, documented on clinical exam (past or present) Presence of olfactory loss or cardiac sympathetic denervation on MIBG scintigraphy
"Red flags"	Rapid progression of gait impairment requiring regular use of wheelchair within five years of onset Total absence of motor symptom/sign progression over five or more years, unless the stability is treatment-related Early bulbar dysfunction: severe dysphonia or dysarthria (speech unintelligible most of the time) or severe dysphagia (requiring soft food, NG tube, or gastrostomy feeding) within first five years Inspiratory respiratory dysfunction: either diurnal or nocturnal inspiratory stridor or frequent inspiratory sighs Severe autonomic failure in the first five years of disease, such as: • Orthostatic hypotension (orthostatic decrease of blood pressure within three minutes of standing by ≥30 mm Hg systolic or ≥15 mm Hg diastolic) in the absence of dehydration, medication, or other diseases explaining autonomic dysfunction • Severe urinary retention or incontinence (nonfunctional) in the first five years of disease (excluding long-standing or small-amount stress incontinence in women). In men, urinary retention is not from prostate disease and must be associated with erectile dysfunction Recurrent (more than once per year) falls from impaired balance within three years of onset Disproportionate anterocollis (dystonic) or contractures of hand or feet within the first 10 years Absence of common non-motor PD features, despite five years disease duration. Includes sleep dysfunction (sleep-maintenance insomnia, excessive daytime somnolence, symptoms of REM sleep behavior disorder), autonomic dysfunction (constipation, daytime urinary urgency, symptomatic orthostasis), hyposmia, or psychiatric dysfunction (depression, anxiety, hallucinations) Otherwise-unexplained pyramidal tract signs, defined as pyramidal weakness or clear pathologic hyperreflexia (excluding mild reflex asymmetry and isolated extensor plantar response) Bilateral symmetric parkinsonism: patient/caregiver report of bilateral symptom onset without side predominance confirmed by objective exam Prominence of postural instability early in the course of the disease

[a]Exclusion of this criterion does not imply dopaminergic functional imaging is required for diagnosis. If no imaging has been performed, this criterion does not apply.
MDS-UPDRS = Movement Disorder Society-Unified Parkinson Disease Rating Scale, MIBG = meta-iodobenzylguanidine, NG = nasogastric.

Source: [65] *Table 6*

- Symptoms that emerged, their sequence, and perceived anatomical involvement, including symptoms that suggest bradykinesia, rigidity, resting tremor, and/or postural instability
- The presence and onset of pre-motor symptoms:
  - Neuropsychiatric symptoms
  - Autonomic dysfunction
  - Sleep disorders
  - Sensory symptoms
  - Fatigue
- Past and present medical disorders
- Family history, including neurologic disorders and ethnic ancestry, as monogenic forms of PD are more frequent in some ethnic groups (e.g., *LRRK2* in Ashkenazi Jews and North African Arabs)
- Exposure to illicit drugs associated with parkinsonism (e.g., methamphetamine, amphetamine)
- Environmental toxin exposure (e.g., manganese in welders)

It is also important to explore the possibility of prescription drug-induced parkinsonism, one of few reversible causes of the disorder. This can be identified by a thorough review of the medication history, paying particular attention to potential drug side effects and the time course of usage in relation to onset of parkinsonian symptoms. The drugs implicated in drug-induced parkinsonism are typical antipsychotics (e.g., haloperidol, chlorpromazine), most atypical antipsychotics (e.g., risperidone, olanzapine), and centrally acting agents used to treat gastrointestinal symptoms (prochlorperazine, promethazine, and metoclopramide). Less common causes are tetrabenazine, reserpine, methyldopa, flunarizine, cinnarizine, verapamil, valproic acid, and lithium. In a study of 155 cases of drug-induced parkinsonism diagnosed between 1995 and 2009, 70% developed symptoms within three months of beginning the prescribed medication; the remaining patients developed symptoms within one year on the offending drug [77]. Recovery from drug-induced parkinsonism can be expected following discontinuation of the medication, though many weeks to months may be required for full resolution of symptoms.

The propensity for antipsychotic drugs to produce parkinsonian side effects has implications for managing patients with PD who experience psychosis as a complication of the disease. For such patients, some have recommended using clozapine, with quetiapine as a second-line option [1].

NEUROLOGIC EXAMINATION

A neurologic examination is performed to provide objective evidence of motor symptoms in the absence of other abnormalities. Simple observation will often reveal a generalized slowness and lack of spontaneous movement. Physical exam findings of parkinsonism motor features supported by the patient's history confirm a diagnosis of idiopathic PD. Patients with idiopathic PD exhibit some combination of the following features, and motor symptom findings are usually asymmetrical [68].

Bradykinesia

To assess bradykinesia, ask the patient to perform repetitive movements as quickly and widely as possible, such as opening and closing the hand, tapping thumb and index fingers, or tapping the foot on the ground. Progressive slowness and/or loss of amplitude should emerge and may bring movement to full arrest (freezing). To globally assess bradykinesia, observe spontaneous movements while the patient is sitting, standing up from a chair, or walking [67; 69]. To avoid misdiagnosis, distinguish clinical bradykinesia from simple slowness in patients with decreased muscle power, spasticity, or reduced motivation in depression or in normal elderly populations that reflect non-specific slowness [67; 69].

Rigidity

Rigidity refers to "leadpipe" resistance, whereby velocity-independent resistance to passive movement is not influenced by inability to relax (i.e., distinct from spasticity). This resistance is felt throughout the full range of movement, and unlike spasticity, it does not increase with higher mobilization speed. When resting tremor co-occurs with rigidity, "cog-wheel rigidity" can be felt during passive limb mobilization, especially in the wrist. When assessing rigidity, interruption of passive movement by a "cog-wheel" movement reflects the underlying 4–6 Hz tremor oscillation. In contrast, pyramidal tone (spasticity) is dependent on the velocity of passive movement, described as ''clasp knife'' in quality because of the higher resistance during early acceleration of the passive movement followed by giving way, such as is seen when opening lock-blade knives [67]. Rigidity is assessed by passive movement of a joint and reinforced by asking the patient to move the opposite limb in a circular motion or open/close a fist.

Tremor

Resting tremor is often observed in patients with PD, and postural tremor and re-emergent resting tremor may be seen with arms outstretched. Resting tremor is best observed in the hands during patient focus on a mental task (e.g., eyes-closed countdown from 100) that facilitates muscle relaxation; in the legs with the patient seated on the edge of an exam table, with legs hanging and feet unsupported; and in the jaw when the patient is engaging another part of the body in activity [4; 67].

Gait

Gait may be stooped or shuffling, with reduced arm swing. Patients often turn en bloc, requiring numerous steps to complete a 180° turn. The pull test (briskly pulling the patient backwards while standing) may be used to assess postural reflexes. Loss of postural reflexes generally occurs in later-stage disease.

DIAGNOSTIC CONFIRMATION

Unless signs or symptoms are observed that are inconsistent with idiopathic PD (i.e., MDS absolute exclusion criteria or red flags), no further testing is needed with history and exam findings consistent with idiopathic PD. Imaging tests are used only to confirm absolute exclusion criteria findings or to rule out or confirm red flag findings [65].

However, there are a variety of special procedures available that help to confirm diagnosis, obtain additional information on disease type or severity, and differentiate PD from disease mimics (***Table 7***). Dopaminergic challenge tests that elicit objective improvement in motor function and alleviation of symptoms provide positive evidence for the diagnosis, although support is not universal [68; 78]. Olfactory testing can help substantiate a PD diagnosis, is inexpensive, is extensively validated, and contributes to the early diagnosis and differential diagnosis of PD. Although it can help identify patients with premotor symptoms of PD, use alone is not diagnostic [1; 68; 79].

The American College of Radiology recommends non-contrast magnetic resonance imaging (MRI) of the head in patients with Parkinson disease with typical clinical features and responsive to levodopa only for problem-solving purposes.

(https://acsearch.acr.org/docs/69360/Narrative. Last accessed April 28, 2025.)

Strength of Recommendation: 7 (Usually appropriate)

Recommendations for genetic testing in diagnosing PD are inconsistent. Some consider genetic testing of questionable benefit due to lack of clarity on which populations to test, the consequences of test results, and cost issues [1]. Others highly recommend use of genetic testing to identify parkinsonism and PD genotypes that differ in clinical course, prognosis, and treatment response from idiopathic PD [68; 79].

EFNS/MDS-ES RECOMMENDATIONS FOR DIAGNOSTIC INSTRUMENT USE IN PARKINSON DISEASE		
Diagnostic Modality	**Level of Evidence**	**Indications for Use**
Genetic testing		
SNCA gene point mutations and multiplication	B	PD families suggestive of dominant inheritance
LRRK2 and known pathogenic variants	B	Typical PD with family history suggestive of dominant inheritance Sporadic PD from specific populations with known founder effect mutations
GBA mutations	B	Founder effect mutations in PD cases in specific populations (e.g., Ashkenazi Jewish) with or without positive family history
Parkin, *PINK1*, *DJ-1* mutations	B	PD with onset before 50 years with family history suggestive of recessive inheritance Sporadic PD with onset before 40 years
ATP13A2, *PLA2G6*, *FBX07*	B	Very early onset PD cases
Olfactory tests		
University of Pennsylvania Smell Identification Test (with other diagnostic tests)	A	PD versus atypical and secondary parkinsonism
	A	Idiopathic PD versus recessive PD forms
	A	Pre-motor PD
Neuropsychologic testing		
Collateral history from a carer, cognitive assessment, and screening of REM sleep behavior disorder, psychosis, severe depression	A	During initial evaluation to exclude other causes of parkinsonism in patients with suspected PD
Transcranial sonography		
Use with other diagnostic tests	A	Differential diagnosis of PD from atypical and secondary parkinsonism
	A	Early diagnosis of PD
	A	Detection of subjects at risk for PD
Magnetic resonance imaging (MRI) in differential diagnosis		
Conventional 1.5-Tesla MRI	A	Differential diagnosis of multisystem atrophy from PD
	B	Differential diagnosis of progressive supranuclear palsy from PD (detection of midbrain atrophy and/or SCP atrophy)
	C	
1.5-Tesla diffusion-weighted MRI	A	Differential diagnosis of multisystem atrophy from PD (identification of putaminal diffusivity changes)
	B	Differential diagnosis of progressive supranuclear palsy from PD (identification of SCP diffusivity changes)
Single photon emission tomography (SPECT) in differential diagnosis		
^{123}Ioflupane SPECT	A	Differential diagnosis of essential tremor from PD and atypical parkinsonism
^{123}I-MIBG SPECT	A	Differential diagnosis of PD from multisystem atrophy
EFNS/MDS-ES = European Federation of Neurological Associations/Movement Disorders Society–European Section, MIBG = meta-iodobenzylguanidine, SCP = superior cerebellar peduncle. Levels of evidence: A = effective, B = probably effective, C = possibly effective.		
Source: [68]		*Table 7*

Some have suggested assessing all patients younger than 40 years of age with suspected PD for Wilson disease. Wilson disease is confirmed by low serum ceruloplasmin, elevated 24-hour urine copper, or the presence of Kayser-Fleischer rings on slit-lamp examination [78].

SCREENING TESTS

Screening tests are used to help identify common comorbidities, including depression and dementia in patients with PD. The American Academy of Neurology (AAN) recommends the following assessment tools when screening for comorbid conditions [80; 81]:

- Depression: Beck Depression Inventory (BDI), Hamilton Depression Rating Scale (HDRS), Geriatric Depression Scale (GDS)
- Dementia: Cambridge Cognitive Examination (CAMCog), Mini-Mental State Examination (MMSE), Montreal Cognitive Assessment (MoCA)

The MDS-UPDRS is widely used in research and in clinical practice to standardize the neurologic exam and present the findings as a pre-determined Likert scale. The UPDRS can be used to assess the clinical status of patients with PD during follow-up. This instrument assesses motor features, psychologic features, activities of daily living, and treatment complications. Increases of 2.5 and 4.3 points in UPDRS motor and total scores, respectively, indicate clinically relevant change [82; 83].

If cognitive impairment is noted on mental status examination, magnetic resonance imaging (MRI) and neuropsychologic testing should be used to distinguish PD with dementia from other neurodegenerative disorders [1].

DIFFERENTIAL DIAGNOSIS

The diagnostic assessment of a patient suspected of having PD should include consideration of other, possibly reversible, disorders that may present with motor signs of parkinsonism. These are often referred to as "atypical" PD or "mimics" of PD and include [67; 69]:

- Essential tremor
- Neurodegenerative syndromes:
  - Multisystem atrophy
  - Progressive supranuclear palsy
  - Corticobasal degeneration
  - Dementia with Lewy bodies
- Symptomatic syndromes of non-neurodegenerative underlying cause:
  - Drug-induced parkinsonism
  - Vascular parkinsonism (i.e., ischemia/infarcts in the basal ganglia)
  - Infectious disease (e.g., acquired immunodeficiency syndrome, subacute sclerosing panencephalitis, postencephalitic parkinsonism, prion disease)
  - Neurotoxin exposure (e.g., carbon monoxide, manganese, MPTP)
  - Structural disorder (e.g., tumor, hydrocephalus, subdural hematoma, trauma)
  - Metabolic disease (e.g., Wilson disease, hypothyroidism)
- Other secondary causes

Assessment

Clues from the medical history and atypical exam findings should prompt a careful work-up to rule out or confirm an alternate diagnosis. The most common syndromes mimicking PD are essential tremor, vascular parkinsonism, Lewy body dementia, progressive supranuclear palsy, multisystem atrophy, corticobasal degeneration, and drug-induced parkinsonism (***Table 8***). Neurologic consultation and neuroimaging studies are often needed to adequately assess many of these possibilities [1; 2; 68; 84; 85].

SYNDROMES THAT MAY MIMIC PARKINSON DISEASE		
Syndrome	**Signs/Symptoms Resembling Parkinson Disease**	**Differentiating Tests**
Essential tremor	Appears or worsens with movement Symmetrical presentation Affects distal extremities, head, and voice Family history common	Improves with alcohol and/or beta-blockers Dopamine transporter scan
Vascular parkinsonism	Symmetrical lower body manifestation Gait highly affected Rest tremor uncommon Cognitive impairment	Poor levodopa response Significant small vessel disease or basal ganglia lacunar infarct(s) on brain MRI Dopamine transporter scan
Drug-induced parkinsonism	Akinesia and bradykinesia	Patient medication history, particularly for dopamine antagonists (e.g., clozapine)
Lewy body dementia	Dementia Vivid visual hallucinations Marked fluctuating mental status	History may be sufficient for diagnosis Neuropsychologic testing to distinguish domains of cognitive deficits Dopamine transporter scan to distinguish from non-Lewy body dementias (e.g., Alzheimer disease)
Progressive supranuclear palsy	Gaze palsies Early falls within one year of diagnosis	Neurologic examination findings of vertical gaze palsy and significant postural instability Evidence of midbrain atrophy on brain MRI (suggestive, not definitive)
Multisystem atrophy	Autonomic dysfunction with symptomatic hypotension, constipation, urinary urge incontinence, fecal incontinence, urinary retention, persistent erectile dysfunction Speech or bulbar dysfunction Pyramidal or cerebellar dysfunction	Poor levodopa response Neurologic examination findings of deficits outside the extrapyramidal system Pontine and cerebellar atrophy on brain MRI (suggestive, not definitive) Electromyography findings of denervation and re-innervation of rectal sphincter muscle
Corticobasal degeneration	Apraxia Alien limb phenomenon Cortical sensory loss	No tests required

Source: [1; 2; 68; 84; 85] *Table 8*

Importance of Establishing a Diagnosis

Determining the presence of parkinsonism is the first step in considering therapeutic options for PD and distinguishing PD from other central nervous system pathologic states. Although exclusion of alternative diagnoses may not expand options for disease-modifying or curative therapies, arriving at a definitive diagnosis is important for purposes of patient and family education, prognosis, reassurance, and options for therapy. A definitive diagnosis gives a name to the condition. This is very important for the patient experience and helps in coming to terms with a chronic disease. An "atypical parkinsonism" or "parkinsonian syndrome" diagnosis leaves patients and family with vague uncertainty and fails to provide a clear basis for management decisions and prognosis. A hierarchical list of diagnostic possibilities should be discussed if definitive diagnosis is elusive. Diagnostic criteria for progressive supranuclear palsy, cortico-basal degeneration, and multisystem atrophy allow for possible and probable diagnostic categories, according to diagnostic certainty [4].

TREATMENT OF PARKINSON DISEASE

Although no cure for PD is yet available, some degree of disease modification and significant alleviation of motor symptoms can be achieved with drug combinations that enhance tissue levels of dopamine, thereby promoting dopaminergic activity. Treatment strategies for PD are influenced by stage of disease, problematic symptom profile, and patient age. Clinical decision-making should balance possible efficacy with potential side-effect risk for each treatment option. Treatment decisions should be based on the best available evidence for each intervention. Pharmacotherapy should be accompanied by non-medical interventions, as needed, for gait and balance dysfunction, vocal impairment, and other motor, non-motor, and comorbid conditions [79].

Management of PD begins at the time of diagnosis but may not require immediate initiation of drug therapy. Early issues for consideration include information delivery, sources of support, counseling to facilitate a realistic view of what to expect going forward, discussion of prognosis, and potential treatment options. These conversations usually take place over several visits and should include discussion of available medical therapies for PD. When possible, these initial meetings should include family members [4].

OVERVIEW OF TREATMENT APPROACHES THROUGH DISEASE PROGRESSION

Initial treatment of early PD generally involves monotherapy, and motor control problems can be improved in many patients. Treatment of later PD becomes more complicated, with disease progression and prolonged dopaminergic drug administration. Requirements for dopamine replacement therapy become increasingly demanding as motor signs worsen. Patients initially well controlled using dopamine agonists require initiation of levodopa and, over time, increasing amounts given in higher doses with more frequent intervals. Patients initiated on levodopa will require the addition of dopamine agonists and/or other adjuncts that improve response to levodopa [86].

The decision to initiate levodopa treatment for PD is guided by clinical need; one should use the lowest dose that achieves a satisfactory clinical response. Levodopa therapy is commonly deferred until motor symptoms interfere with the patient's purposeful motor function. This is based on the assumptions that:

- The period of improved motor control is finite, and levodopa therapy is more valuable in later disease, when symptom improvement is greater.
- Deferring levodopa initiation delays the onset of dyskinesias.
- Early symptomatic treatment has no effect on disease course.

A five-year, randomized cohort study, designed to elucidate whether early use of levodopa has any fundamental impact on the course of PD, found no evidence that early treatment slows progression of disease [87]. Neither is there any reason to delay once treatment with levodopa is indicated. There is evidence that for early PD, a levodopa dose less than 400 mg/day minimizes the risk of drug-associated dyskinesia; moreover, early use of levodopa has been shown to be the most effective way to alleviate motor symptoms. It appears that progression of PD has a greater impact on development of levodopa-induced dyskinesia than medication duration itself [86; 88; 89].

Some PD motor symptoms show preferential dopaminergic response. For example, bradykinesia and rigidity show the most robust levodopa response. Rest tremor severity correlates poorly with the other cardinal symptoms and extent of dopamine neuron loss and inconsistently responds to dopaminergic therapy. This sign may originate from a trigger in the basal ganglia, with contributions from cerebellothalamic pathways. Freezing gait and imbalance with frequent falls also poorly respond to dopaminergic treatment [8].

Added complexity comes with progression from later to advanced PD. The onset of motor fluctuations and motor complications (e.g., dyskinesia, freezing) create the greatest challenge to treatment efforts to maintain mobility and function in earlier disease. Predicting the onset of motor complications and fluctuations in individual patients is very difficult, but disease duration and stage, dose and duration of levodopa exposure, sex, and body weight are contributing factors [86].

Even if motor symptoms are well controlled, numerous non-motor components of PD will emerge and can be intensely burdensome to patients. Many non-motor symptoms lack response to dopaminergic medications, reflecting progression beyond the dopamine neuron motor system and extensive disease involvement in the cortical and frontal lobes and widespread central neuropathology. Only recently have non-motor symptoms received adequate research attention, and for some of these syndromes, effective treatments have been identified and become available or their final regulatory evaluation is in progress [82; 86].

MEDICATION NON-ADHERENCE

An important issue, unaddressed by practice guidelines, is medication non-adherence in patients with PD. While the prevalence of non-adherence broadly varies by assessment method, the figures range from 15% to 20% using patient self-report to 67% or more using pharmacy refill data and pill counts [90]. An important dimension in PD treatment is timing adherence, as dopaminergic medications should be taken at precise and evenly spaced intervals, as instructed by the prescribing physician. Non-adherence to timing of dosage is probably very common and contributes to unwanted dopamine variability implicated in earlier onset of motor fluctuations [91]. The overall consequence of non-adherence is unsatisfactory motor control, with diminishing mobility, greater fluctuations, dyskinesias, and declining quality of life [92].

In chronic diseases, highest medication adherence occurs with once-daily formulations, but this sharply decreases with each added daily dose [93]. Polypharmacy in PD is normative, with most patients taking two or more antiparkinsonian drugs and additional medications for non-motor symptoms and comorbidities. In addition to the risk of non-adherence that directly correlates with the number of prescriptions and daily doses per prescription, many patients with PD experience depression and/or cognitive impairment, both of which are strong independent risk factors for medication non-adherence [92].

Medication non-adherence among patients with PD should be recognized as a common, under-reported, detrimental, and costly cause of suboptimal disease control. Reliance on clinical judgment to identify non-adherence is demonstrably inaccurate, and healthcare professionals should use nonjudgmental interviewing skills that encourage patient admission of their non-adherence without fear or concerns of disapproval or termination of care. Barriers to adherence should be explored and clinical resources applied to surmount them. These include simple explanations of how medications optimally work when taken correctly and referral to non-adherence counseling. To avoid unnecessary dose escalations, adverse effects, and increased patient and healthcare costs, non-adherence should be explored before a drug regimen is deemed ineffective [92].

PHARMACOTHERAPIES

Levodopa

Exogenous dopamine administration is ineffective for treatment of PD, because circulating dopamine does not cross the blood-brain barrier so as to reverse brain dopamine depletion. Levodopa is a dopamine prodrug able to cross the blood-brain barrier where it is converted to dopamine by aromatic amino acid decarboxylase (AAAD). The regular administration of oral levodopa leads to repletion of dopamine in the substantia nigra pars compacta, and to storage in presynaptic dopamine neurons for subsequent use. The majority of patients treated with levodopa realize significant and prolonged improvement in

motor function, though there are side effects and, in time, many patients experience fluctuations in beneficial effects of the drug. Levodopa was introduced for use in PD in the late 1960s, and remains the criterion-standard treatment [8].

The bioavailability of orally administered levodopa is reduced by extensive metabolism to dopamine in the gut. Only 30% of an oral dose reaches systemic circulation for distribution to the brain. For this reason, Levodopa used to treat PD is always combined with carbidopa, a peripherally acting AAAD inhibitor. Carbidopa inhibits peripheral conversion of levodopa to dopamine, which triples levodopa bioavailability and lowers the dosage requirements. Carbidopa 75–100 mg/day is the dose needed to inhibit peripheral conversion of levodopa to dopamine. Carbidopa also helps to diminish acute peripheral dopamine side effects, such as nausea, vomiting, and hypotension, and improves tolerability [94].

The risk for side effects and toxicity, including troublesome dyskinesia, is high in patients on chronic levodopa therapy. For this reason, careful dose titration and tight adherence to the effective dose is important for PD symptom management. No evidence has been found that using an extended-release levodopa/carbidopa formulation, or adding a catechol-*O*-methyltransferase (COMT) inhibitor, delays or prevents the development of motor fluctuations [95].

Because levodopa is absorbed in the proximal small intestine, food may delay absorption. Levodopa also competes with dietary proteins for transport into the brain. High-protein meals should be kept separate from levodopa dosing, and daily dietary protein intake should be reduced to approximately 0.8 g/kg (of body weight). Levodopa is metabolized in the gastrointestinal tract, kidneys, and liver, with 70% excreted in the urine. Levodopa half-life is roughly one hour. Dosing should be reduced 10% to 30% when other dopaminergic agents are added to carbidopa/levodopa. Available formulations in the United States are [94; 96]:

- Carbidopa/levodopa tablet (Sinemet)
- Carbidopa/levodopa orally disintegrating tablets (Parcopa ODT, Dhivy)
- Carbidopa/levodopa oral extended-release capsule (Crexont)
- Carbidopa/levodopa sustained-release tablet (Sinemet CR)
- Carbidopa/levodopa extended-release tablet (Rytary ER)
- Carbidopa/levodopa enteral suspension (Duopa)
- Carbidopa/levodopa/entacapone (Stalevo)

Potential adverse events associated with levodopa/carbidopa can be generally categorized as CNS, gastrointestinal, or other. Adverse effects involving the CNS include confusion, sedation, vivid dreams, dizziness, hallucinations, psychosis, and depression. Gastrointestinal effects may include nausea, vomiting, and changes in bowel habits. Orthostasis, leg edema, dyskinesia, dystonia, hemolytic anemia, and leukopenia may also occur. All patients taking levodopa should be monitored for changes in blood pressure, pulse, mental status, and clinical response.

With prolonged therapy and disease progression, the duration of benefit from each levodopa dose often becomes increasingly shorter. "End of dose deterioration," "wearing-off," "off periods," or simply "off" refers to the waning or absent effects of levodopa within four hours of the last dose. As "off" periods increase, "on" periods (levodopa-related motor symptom control) decrease [4].

Caregivers monitoring the course of a stable patient on chronic levodopa therapy for PD often face two potential therapeutic challenges. First is the development of dyskinesia, indicative of drug intolerance or excessive dosage. The second is fluctuation in motor symptoms, perhaps indicative of inadequate dosage, failing compliance, or waning therapeutic effectiveness. The frequency, or risk, of dyskinesia and motor fluctuations during chronic levodopa therapy for PD is difficult to predict. One literature review of publications spanning 1966 through 2000 showed

that among patients receiving levodopa therapy, the median frequency of dyskinesia was 39%, and after a satisfactory first year of therapy, the frequency of motor fluctuations gradually increased to 40% of patients by four to six years of treatment [97].

Dopamine Agonists

Dopamine D2/3 receptor agonists bind post-synaptic striatal dopamine receptors to increase dopaminergic neurotransmission and reduce parkinsonism symptoms. Ropinirole (oral), pramipexole (oral), and rotigotine (transdermal) are the most widely used agents. In advanced disease, subcutaneous apomorphine is continuously delivered via external pump or is used for rapid rescue therapy (via injection). The ergot derivative dopamine agonists cabergoline, pergolide, and bromocriptine are not recommended as first-line dopamine agonist therapy, and bromocriptine is associated with the development of fibrotic tissue. Pergolide was withdrawn from the U.S. market due to increased risk of cardiac fibrosis [98]. Ergot derivatives require specialized side effect monitoring, but they remain options for patients lacking benefit or tolerability with other dopamine agonists [79; 99].

Dopamine agonists are the second most potent drug class (after levodopa) for motor symptom control in PD and are effective at all stages of the condition. Initial dopaminergic therapy using dopamine agonists (versus levodopa) is associated with reduced/delayed treatment-related complications, such as levodopa-induced dyskinesia and motor fluctuations [8; 100]. Due to side effects of long-term treatment with levodopa, initiation of treatment with dopamine agonist monotherapy is now recommended in young patients to postpone therapy with levodopa and the subsequent development of extrapyramidal side effects [101; 102].

However, poor tolerability can limit the use of dopamine agonists. While dopamine agonists are less likely to lead to motor fluctuations in early disease than levodopa, they are less effective for motor symptoms and carry greater risk of side effects such hallucinations, psychosis, hypotension, peripheral edema, excessive daytime somnolence, and impulse control disorders. In patients older than 70 years of age, dopamine agonists should be used with caution or avoided entirely [95]. All patients taking ropinirole, pramipexole, or rotigotine should be monitored for changes in blood pressure, daytime alertness, weight, and heart rate [94].

Ropinirole

Ropinirole undergoes hepatic metabolism, with a half-life of about six hours. It is associated with various adverse effects in various systems, including the gastrointestinal system (e.g., nausea, vomiting, dyspepsia, abdominal pain, constipation) and the CNS (e.g., dizziness, somnolence, headache, syncope, confusion, hallucinations, impulse control disorders, sleep attacks). Other potential adverse effects include fatigue, asthenia, dependent/leg edema, viral infection, pain, increased sweating, orthostatic symptoms, pharyngitis, abnormal vision, and urinary tract infection [94].

Pramipexole

Pramipexole is administered orally for PD and is available in immediate- and extended-release formulations. The half-life in healthy adults is about 8 hours, but this is extended to 12 hours in elderly patients. It is excreted in the urine primarily as unchanged drug, and dose adjustment is required in renal impairment. Overnight switch from immediate- to extended-release is successful in 80% of patients [94]. Potential adverse effects include nausea, abdominal pain/discomfort, constipation, dizziness, somnolence, headache, hallucinations, impulse control disorders, dyskinesia, orthostatic hypotension, xerostomia, peripheral edema, and muscle spasms [94].

Rotigotine

Rotigotine is available as a transdermal patch for the treatment of PD. It undergoes extensive metabolism via conjugation and *N*-dealkylation. The initial half-life is three hours, with the terminal half-life five to seven hours after patch removal. Potential adverse effects have included nausea, vomiting, somnolence, dizziness, application-site reactions, dyskinesia, anorexia, hyperhidrosis, visual disturbance, and peripheral edema, and all patients should be monitored for skin reactions. Patients with sulfa allergy should not be prescribed rotigotine, and patches contain aluminum and should be removed prior to MRI [94].

Apomorphine

Apomorphine for PD is given as a subcutaneous injection into the abdominal wall, upper arm, or upper leg; the injection site should be rotated. It is indicated for hypomobility and "off" episodes associated with PD.

Apomorphine undergoes extensive first-pass metabolism, with a terminal half-life of about 40 minutes. Nausea, vomiting, drowsiness, somnolence, dizziness, orthostatic hypotension, hallucinations, confusion, dyskinesia, rhinorrhea, and edema/swelling of extremities may occur. It is important to avoid use of apomorphine with serotonin blockers, as co-ingestion may cause profound hypotension. All patients taking this agent should be monitored for orthostatic hypotension and drowsiness [94].

Bromocriptine Mesylate

Bromocriptine mesylate is taken orally and is metabolized by the liver. The half-life is approximately 5 to 15 hours. Potential adverse effects include nausea, vomiting, abdominal discomfort, abnormal involuntary movements, ataxia, hallucinations, confusion, "on-off" phenomenon, dizziness, syncope, drowsiness, insomnia, depression, visual disturbance, hypotension, shortness of breath, constipation, vertigo, and asthenia. Long-term treatment with this drug is associated with pleural thickening (fibrosis). As such, patients' pulmonary function should be monitored during treatment [94].

Monoamine Oxidase B Inhibitors

MAO-B is an enzyme that inactivates dopamine by breaking it down into metabolic byproducts. MAO-B inhibitors block the breakdown of dopamine, slowing the loss of dopamine and several of the effects of PD. MAO-B inhibitors are generally considered for initial treatment of early PD as monotherapy and as adjunctive therapy to augment the effects of levodopa in later PD. The preferred agents are selegiline and rasagiline, both of which have shown symptomatic benefit and multiple neuroprotective effects in pre-clinical research [8; 95; 103].

Selegiline

In the treatment of PD, selegiline may be used as monotherapy (off-label use) or combined with levodopa. This agent blocks the breakdown of dopamine via MAO-B inhibition. It is metabolized via CYP450 enzymes to amphetamines, with a half-life of 10 hours. In high doses, it may precipitate a hypertensive crisis. Other potential adverse effects include nausea, weight loss, dyspepsia, hypotension, decreased heart rate, headache, hallucinations, vivid dreams, dizziness, insomnia, flu-like symptoms, dyskinesias, dystonia, rash, and photosensitivity [104]. All patients undergoing treatment with selegiline should be monitored for rash, drug interactions, and changes in blood pressure, cardiac status, and mental status (i.e., increased anxiety) [104].

In addition to a capsule/tablet, selegiline is available as an orally disintegrating tablet and a transdermal 24-hour patch. Pharmacology, potential adverse effects, and monitoring are similar, but metabolism of the disintegrating tablet bypasses the liver to reduce formations of amphetamine metabolites, which reduces the risk of insomnia side effects [104].

Rasagiline

Oral rasagiline may be used in monotherapy or combination therapy for patients with PD. This agent inhibits the breakdown of dopamine via MAO-B inhibition and is metabolized via CYP1A2. The half-life is three hours. The potential adverse effects and patient monitoring requirements are the same as with selegiline [104].

Catechol-O-Methyltransferase Inhibitors

COMT is an enzyme that converts levodopa in peripheral circulation to 3-O-methyl-DOPA (3-OMD). This metabolite cannot be converted to dopamine and accumulates in plasma during levodopa therapy. Inhibition of COMT increases the bioavailability of levodopa, allowing a larger amount of the drug to reach the brain and consequently raise dopamine levels. COMT inhibitors are always taken in combination with levodopa because they lack intrinsic dopaminergic activity. They are used in PD to potentiate levodopa effects when "wearing off" or other motor complications appear during carbidopa/levodopa therapy [104].

Entacapone

As a COMT inhibitor, entacapone inhibits the peripheral metabolism of levodopa. It is metabolized to active isomer and undergoes glucuronidation to inactive metabolites, with a half-life of two hours. Potential adverse effects include exacerbation of levodopa adverse effects, brown/orange urine, and diarrhea. All patients should be monitored for changes in blood pressure and mental status. A fixed-dose combination of entacapone with carbidopa/levodopa is available and reduces the number of tablets needed for treatment, which may improve adherence [104].

Tolcapone

Tolcapone inhibits peripheral and central metabolism of levodopa. It has a half-life of about three hours and is metabolized via glucuronidation and CYP2A6 and CYP3A4 enzymes. The adverse effects are the same as those described for entacapone, plus transient elevations in liver enzymes and fulminant liver failure. In addition to the monitoring recommended for entacapone, these patients should be regularly tested for liver enzymes and function [104].

Opicapone

Opicapone is a novel, once-daily, third-generation COMT inhibitor. Research has compared opicapone with entacapone and placebo as a levodopa adjunct. In a study involving 590 patients with PD-associated motor fluctuations, the mean reduced times in "off" state were 56 minutes for placebo, 96.3 minutes for entacapone, and 116.8 minutes for opicapone after 14 to 15 weeks. Opicapone 50 mg was statistically superior to placebo and non-inferior to entacapone, but lower-dose opicapone did not differ from placebo [105].

The most common adverse events with opicapone are dyskinesia, insomnia, and constipation. Serious adverse events were reported in six patients with placebo, eight with entacapone, and four with opicapone 50 mg. In addition to "off" time efficacy, an advantage of opicapone is the once daily dosing [105].

Anticholinergic Agents

Anticholinergic agents used in PD treatment include benztropine (Cogentin) and trihexyphenidyl. Anticholinergics may be helpful as a symptomatic treatment in younger patients with early PD and severe tremor or dystonia, but they should not be drugs of first choice due to their narrow range of efficacy. Adverse effects from nonselective cholinergic receptor blockade are a major drawback and include CNS-related side effects of cognitive impairment, exacerbation of dementia, delirium, sedation, and hallucinations. Other side effects include constipation, xerostomia, blurred vision, and urinary retention; higher doses may cause or worsen orthostatic hypotension and palpitations. Elderly patients are especially prone to these side effects plus confusion and memory difficulties, and anticholinergic agents are not recommended in this population [95].

Amantadine

Amantadine is an *N*-methyl-d-aspartate (NMDA) antagonist with modest benefit in early PD and efficacy in suppressing levodopa-induced dyskinesia in later/advanced PD. The mechanism of action is thought to involve augmentation of pre-synaptic dopamine release and NMDA glutamatergic antagonism. Common side effects include pedal edema and livedo reticularis (violet, lace-like coloration) [8].

Amantadine is the only agent demonstrated to suppress levodopa-induced dyskinesia without worsening parkinsonism, and the American Academy of Family Physicians recommends that amantadine should be considered for treatment of dyskinesias in patients with advanced PD [2]. However, use in frail elderly patients with advanced PD may result in confusion, hallucinations, and/or worsening motor symptoms [106].

Acetylcholinesterase Inhibitors

The acetylcholinesterase inhibitor rivastigmine is the only drug approved by the U.S. Food and Drug Administration (FDA) for the treatment of mild-to-moderate PD dementia. Other approved drugs for dementia, including donepezil, galantamine, and memantine, have been evaluated for the treatment of PD dementia, but their efficacy has not been clearly shown [106].

Rivastigmine has shown significant improvement in PD dementia that was maintained through 48- and 76-week follow-up in different trials. In long-term trials comparing rivastigmine capsules (12 mg/day) versus transdermal patch (9.5 mg/24 hours), the rates of adverse effects from worsening PD were 36.1% with the capsule (tremor in 24.5%) versus 31.9% with the patch (tremor in 9.7%). Both formulations showed a 2.1-point worsening on the UPDRS-III motor scale [107; 108].

Novel and Investigational Agents

Istradefylline

In 2019, the FDA approved istradefylline as an add-on treatment to levodopa/carbidopa in adult patients with PD experiencing "off" episodes [109]. This agent is an adenosine receptor antagonist with evidence of significantly decreasing daily "off" time compared with patients receiving a placebo. Potential side effects include dyskinesia, dizziness, constipation, nausea, hallucination, and insomnia [109].

Adenosine A2A Receptor Antagonists

A2A receptors are co-localized on dopamine D2 receptors and may be over-activated in PD. Thus, A2A receptor antagonism may reduce PD motor symptoms [110]. Istradefylline was the first A2A antagonist evaluated in PD, but it received a "not approvable" letter from the FDA due to lack of clinical benefit and association with dyskinesias. A subsequent review concluded istradefylline 50 mg had clinical potential as a levodopa adjunct in PD, with support from a clinical trial showing significant reduction in "off" time and good tolerance [106; 111].

Riluzole

There has been interest in glutamate receptor antagonists for the treatment of PD based on the finding that PD is linked to glutamate overactivation in basal ganglia circuits, resulting in oxidative stress and cell death. Riluzole, an NMDA receptor antagonist approved for the treatment of amyotrophic lateral sclerosis, was studied in PD, but it lacked significant effects on survival or disease progression [104].

Safinamide

Safinamide is an alpha-aminoamide developed as adjunct therapy to dopamine agonist or levodopa therapy in patients with PD. This drug shows dopaminergic and non-dopaminergic activity, including MAO-B inhibition, sodium channel antagonism, and inhibition of glutamate release. Clinical trials have shown significantly improved motor symptoms versus placebo. In a six-month double blind, placebo-controlled study of patients with mid-to-late stage PD with motor fluctuations, the addition of safinamide 50–100 mg/day was shown to significantly improve "on time" without increasing dyskinesia and to improve motor function, activities of daily living, quality of life measures, and depressive symptoms [112]. Clinical benefit was sustained over an additional 18-month period of continued treatment and observation.

In 2017, the FDA approved safinamide as "add-on" treatment for patients with PD who are taking levodopa/carbidopa and experiencing "off" periods [6].

Cannabidiol

Cannabidiol, the primary non-psychoactive constituent in *Cannabis*, has been evaluated for treatment efficacy in several non-motor PD conditions. In patients with PD-associated psychoses of at least three months' duration, oral cannabidiol treatment ≤400 mg/day for four weeks significantly reduced psychotic symptoms. No cognitive or motor side effects were found in study participants [113].

A small case series of patients with PD and REM sleep behavior disorder examined treatment response to oral cannabidiol 75 mg/day or 300 mg/day for six weeks. In this sample, symptoms of REM sleep behavior disorder included swearing, laughing, yelling, pushing, kicking, or punching during REM sleep, occurring two to seven times per week. After six weeks of cannabidiol, REM sleep behavior disorder symptom frequency was no times per week in 75% and one time per week in 25% of patients. All patients reported elimination of nightmares. Shortly after cannabidiol cessation, symptom frequency returned to baseline level in all patients. No side effects were observed [114].

Inosine

The antioxidant urate precursor inosine has been associated with lower risk of PD and slower PD progression and was suggested as neuroprotective in laboratory assays. The effects of inosine on PD are currently in phase III clinical trial evaluation in the Safety of Urate Elevation in Parkinson Disease (SURE-PD) study [89].

Agents FDA-Approved for Other Indications

In addition to investigational new drugs, several FDA-approved medications have been studied for their off-label use in the treatment of PD. Calcium-channel blockers are one such group. In one study, the calcium-channel blocker isradipine was found to reduce risk of PD in patients 65 years of age or older [115]. Isradipine, a calcium-channel blocker in use as hypertension therapy, may be neuroprotective in PD. The drug is currently in phase III trials (known as STEADY-PD) to determine its utility in treating early PD [89].

Evidence for the role of neuroinflammation in the pathogenesis of PD have prompted trials of several anti-inflammatory agents. Nonsteroidal anti-inflammatory drugs (NSAIDs) may be protective against PD, but the overall evidence of neuroprotective effect with aspirin or NSAIDs in PD is inconsistent [104].

The stimulant methylphenidate has been found in limited studies to improve gait hypokinesia and freezing in patients with PD receiving deep brain stimulation of the subthalamic nucleus [116].

Exenatide is a glucagon-like peptide-1 (GLP-1) receptor agonist used for the treatment of type 2 diabetes. In a 12-month trial of 45 patients with moderate PD, subcutaneous exenatide showed clinically relevant improvements in PD across motor and cognitive measures versus untreated controls [117; 118].

Zonisamide is an anticonvulsant with neurotransmitter effects, including stimulation of dopamine synthesis, and is approved in Japan for the treatment of PD. Use as an adjunct to levodopa found improvements in "off" time [119].

Beta-blockers are considered a therapeutic option for PD tremor, although some patients may not benefit from or tolerate these agents [120].

MANAGEMENT OF EARLY PARKINSON DISEASE

The therapeutic objective in patients with early PD is symptomatic treatment of motor symptoms to restore more normalized motor function and to optimize and maintain patients' ability in perform activities of daily living. Therapy initiation is individualized, based on patient age, handedness, employment status, and functional status. Tremor is often the symptom that brings patients to medical attention and diagnosis, but it is dominant at rest and infrequently a source of disability or reason to initiate treatment. Rigidity and bradykinesia are more frequently associated with the functional limitations and mobility impairments that influence a patient to initiate treatment [8]. Initial therapy should also target the most disruptive and impairing symptoms in each patient, which can differ with tremor versus rigidity [121].

EVIDENCE-BASED PRACTICE RECOMMENDATION

The European Federation of Neurological Societies asserts that the optimal time frame for onset of therapy for Parkinson disease has not been clearly defined. Once parkinsonian signs start to have an impact on the patient's life, initiation of treatment is recommended.

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Level of Evidence: Expert Opinion/Consensus Statement

Initial therapeutic options for motor symptoms, in descending order by potency of effect, are levodopa, dopamine agonists, and MAO-B inhibitors. Dopaminergic agents (levodopa and dopamine agonists) remain the mainstay of symptom control but are not always first-line treatment. The timing of dopaminergic therapy initiation depends on patient preference, degree of disability, and potential side effects. In general, early dopaminergic treatment is recommended, and the choice, depending on age and overall cognition, is between levodopa preparations, dopamine agonists, and MAO-B inhibitors [4]. In 2021, the American Academy of Neurology published guidelines on choice of dopaminergic therapy for motor symptoms in early Parkinson disease [122]. These guidelines discuss the rationale for selecting levodopa vs. dopamine agonists vs. MAO-B inhibitors.

The assumption that dyskinesia strictly arose from long-term levodopa use led to the common practice of delaying its initiation until the onset of significant motor symptoms in order to save the window of efficacy before dyskinesia begins. As noted, it is now thought that disease stage has greater influence than medication duration on development of levodopa-induced dyskinesia. This has led to earlier levodopa initiation, although MAO-B inhibitors or dopamine agonists are often preferred as initial early PD therapy [8].

Treatment-Naïve Patients

The initial choice of drug depends on the likelihood of improving motor function (better with levodopa) compared with the risk of motor complications (more common in younger patients, delayed by agonists) and the presence of neuropsychiatric complications (more common in older and cognitively impaired patients, greater with agonists). Levodopa is the mainstay of initial treatment and the most effective drug for improving motor function. One should avoid controlled-release formulations or adding entacapone, as this is not effective for delaying the onset of motor complications. Other treatments include MAO-B inhibitors (e.g., selegiline, rasagiline) or oral or transdermal dopamine agonists (e.g., pramipexole, ropinirole, rotigotine). Initial treatment with an agonist can be recommended in younger patients. Ergot derivatives (e.g., bromocriptine, cabergoline) are not recommended due to the increased risk of fibrotic development [79]. Amantadine and anticholinergic agents are also options. Rehabilitation in early-stage disease has seldom been evaluated, and therefore a recommendation for or against its use cannot be made [79].

Dose adjustments with dopamine agonists and levodopa preparations are made in response to clinical effect, emerging symptoms, and/or side effects. Risks of psychiatric side effects and dyskinesias are greater at higher doses, and treatment with the lowest dose possible to achieve benefit is favored; this better maintains patient function and quality of life. Patients older than 50 years of age who receive levodopa doses greater than 600 mg/day are more likely to develop dyskinesia [4].

Adjustment of Initial Therapy in Patients without Motor Complications

Patients who initiate treatment with an MAO-B inhibitor, anticholinergic agent, amantadine, or their combination will, at some point, require levodopa or a dopamine agonist added. When patients on dopaminergic therapy require treatment intensification, the options are to increase the dose, switch to another agonist, or add levodopa. Patients

who are initiated on levodopa may be better managed by an increase in the dose, the addition of an agonist, or the addition of a COMT inhibitor [79]. If significant tremor persists in patients with disabling tremor, add or initiate with [79]:

- Anticholinergic drug
- Clozapine
- Beta-blocker (e.g., propranolol)
- Deep brain stimulation

MANAGEMENT OF LATER PARKINSON DISEASE

Later stage PD is clinically characterized by diminished efficacy of dopaminergic therapy and the emergence of motor fluctuations and dyskinesias. The initial response of most patients to carbidopa/levodopa therapy is positive, because at that stage dopaminergic systems are relatively intact and produce sufficient endogenous dopamine to "buffer" the exogenous carbidopa/levodopa. With disease progression, combined effects from dopaminergic neuron loss, receptor alteration, modifications in circuitry, and desensitization of receptors lead to inconsistent and unpredictable carbidopa/levodopa response and the development of motor fluctuations. At some point, nearly all patients with PD develop motor fluctuations that include wearing off, delayed onset dyskinesias, and dystonias [123; 124; 125].

Levodopa-Induced Dyskinesias

While early PD can be effectively managed with levodopa for many years, disease progression invariably leads to peak-dose dyskinesias, including tics, tremors, and other involuntary movements [6]. In addition to levodopa, dyskinesias can also develop with dopamine agonists or MAO-B inhibitors. Men and younger patients have higher risk of dyskinesias. Mild dyskinesias do not require specific treatment, but more severe cases may respond to a reduction in levodopa dose or addition of an NMDA antagonist or dopamine receptor agonist [4].

Motor Complications

Motor complications become the dominate clinical issue when patients develop end-of-dose deterioration (symptom relapse) or peak-dose dyskinesias. Several potential mechanisms contribute to the development of motor complications. Low plasma levels of dopaminergic drugs lead to "off" periods, while high levels increase peak-dose dyskinesia; the levodopa therapeutic window is narrowed. Motor complications accrue in an estimated 10% of patients with PD per year, with an estimated 50% prevalence with five years of levodopa treatment. Other motor signs and symptoms can emerge, including axial motor symptoms of gait and postural abnormalities, that increase the risks of falling, dysphagia, dysarthria, and cognitive problems [6].

Emergence of Motor Symptoms

The common, debilitating axial motor symptoms/signs of late-stage PD are gait impairment, postural instability, and other postural abnormalities. Unlike the cardinal motor symptoms of PD (rest tremor, bradykinesia, and rigidity), axial motor symptoms do not respond well to dopaminergic therapy and physiotherapy. This is likely because motor control of axial and cardinal functions is mediated by different anatomical-functional pathways [70].

Freezing gait often appears later in the disease course and can lead to significant declines in quality of life. Walking requires shifting from one leg to the other, and patients with freezing gait experience a sense of falling every time they lift a foot up off the floor. Every step forward resembles a controlled fall. Research has shown that auditory stimuli (e.g., sound of a metronome) or visual cues (e.g., a flash of light or lines on the floor indicating stride length) can reduce episodes of freezing, but how these cues work is unknown [6].

Management

When motor complications emerge, manipulation of levodopa dose or frequency is often the first strategy, but the initial improvement is eventually precluded by the emergence of dyskinesias.

Levodopa Wearing Off

Studies comparing immediate- and modified-release levodopa found roughly 25% less levodopa absorbed with the modified-release formulation, and this should be considered when switching between preparations. Erratic levodopa absorption in later PD and significant reduction in doses per day with modified-release levodopa can result in delayed or no "on" responses. Modified-release levodopa has greatest benefit in reducing overnight wearing-off [4].

The next strategy is adding adjunctive therapies to levodopa to control fluctuating motor response. Wearing-off symptoms can be reduced by adding MAO-B inhibitors, COMT inhibitors, or dopamine agonists. The MAO-B inhibitor rasagiline reduces "off" time by around 1.5 waking hours per day; the same results were found with the COMT inhibitor entacapone [4]. The COMT inhibitors entacapone and tolcapone can improve CNS delivery of levodopa by inhibiting its peripheral degradation to 3-OMD. Entacapone is most widely used due to rare hepatic failure associated with tolcapone, although the latter agent may be more effective [8; 79]. COMT inhibitors can increase ''on'' time, but these drugs lack intrinsic antiparkinsonism efficacy as monotherapy [4].

The dopamine agonists pramipexole and ropinirole reduce "off" time by around 15% but can cause problematic side effects, including drowsiness, sudden onset of sleep, and impulse control disorders, in 15% or more of patients. Patients should be screened for pre-existing drowsiness and tendencies toward compulsive disorders (e.g., gambling) before prescribing a dopamine agent. Patients should be monitored for the development of impulse control disorders throughout the course of treatment. Apomorphine can be administered by continuous infusion or intermittently to treat sudden "off" periods unresponsive to other medications [4].

Severe Motor Fluctuations

Deep brain stimulation is effective against motor fluctuations and dyskinesia [79]. However, because the risk for adverse events is elevated, this modality is only recommended in patients younger than 70 years of age without major psychiatric or cognitive problems. Other options include subcutaneous apomorphine administered via penject or pump or intrajejunal levodopa/carbidopa enteric gel administered through percutaneous gastrostomy [79].

Unpredictable "On-Off"

Deep brain stimulation of the subthalamic nucleus is effective to manage unpredictable "on-off" symptoms [79]. In treatment studies for wearing-off, patients with unpredictable "on-off" have been excluded or were uncommon. Thus, there is insufficient evidence to conclude if the results are valid for unpredictable "on-off." The strategies described for dyskinesia and wearing-off should be considered. For delayed "on," dispersible levodopa and subcutaneous apomorphine injections have some value [79]. Reducing or redistributing dietary proteins may be helpful, but a more practical approach is to take levodopa on an empty stomach one hour before, or at least one hour after, each meal.

Freezing

Management options for "off" freezing are the same as for wearing-off. However, freezing during "on" often does not respond to dopaminergic strategies. Visual or auditory cues are empirically useful for facilitating the start of motor acts [79].

Dyskinesias

The first step in managing dyskinesias is to reduce the levodopa dose. This elevates the risk of increasing "off," but it can be compensated for by increasing the number of doses or adding a dopamine agonist. MAO-B or COMT inhibitors should also be reduced or discontinued at the risk of worsening wearing-off [79].

Amantadine (an NMDA antagonist) is the sole effective agent in suppressing levodopa-induced dyskinesia without worsening parkinsonism and should be initiated at 200–400 mg/day [79; 106]. In younger patients, an anticholinergic agent may be prescribed [79].

Deep brain stimulation of the subthalamic nucleus also reduces dyskinesia symptoms and dopaminergic dosing. Stimulation of the globus pallidus pars interna may reduce severe dyskinesia.

Clozapine or quetiapine may be added. Clozapine is associated with potential serious adverse events (e.g., agranulocytosis, myocarditis) and requires monitoring. Intrajejunal levodopa infusion is another option. Continuous subcutaneous infusion of apomorphine allows reduction of levodopa [79].

Biphasic Dyskinesia

Biphasic dyskinesias can be very difficult to treat, and well-designed treatment studies are sparse. Deep brain stimulation of the subthalamic nucleus appears effective [79]. The strategies described for managing peak-dose dyskinesias may also be considered.

Another option is increasing the size and frequency of levodopa dosing, at the risk of increasing peak-dose dyskinesia. However, larger and less frequent doses may give more predictable responses. Apomorphine and intrajejunal levodopa infusion may be tried [79].

Off-Period and Early-Morning Dystonias

The strategies for wearing-off can be applied to patients with off-period dystonias. Additional levodopa or dopamine agonist doses at night may be effective if the symptoms are worst in the morning. Deep brain stimulation is recommended, and botulinum toxin injection may be employed [79].

MANAGEMENT OF ADVANCED PARKINSON DISEASE

Advanced PD is defined as the onset of persistent and severe motor complications despite optimized oral pharmacologic and behavioral management [106]. The development of motor complications during later disease progresses to advanced disease. The underlying pathophysiologic mechanisms result in a narrowing therapeutic window whereby low plasma and striatal levels of dopaminergic drugs lead to "off" periods and high levels lead to increases in peak-dose dyskinesia. Patients experience increasing dose failures from absorption problems [8; 106]. Dyskinesias become more frequent and severe in advanced disease, appearing in 59% of patients after 10 years of levodopa treatment. Even small dose increases in levodopa to improve motor function may produce dyskinesias. Management of dyskinesias and "off" periods by lowering the levodopa dose and shortening the time intervals between doses becomes increasingly ineffective in advanced disease [95].

Long-acting dopamine agonists taken once daily have become popular with patients. In theory, long-acting dopamine agonists should allow a stable release of drug, with continuous dopaminergic stimulation reducing plasma fluctuations and decrease motor complications. Many experts state this theory is unsupported by observations in clinical practice, and the presumptive advantage of long-acting dopamine agonists has not been proven. Dopamine agonists should not be prescribed to patients with dementia, hallucinations, autonomic dysfunction, or sleep disorders, and impulse control disorders are a potential side effect with this drug class [106].

With disease progression in advanced PD, the development of wearing-off symptoms and dyskinesias can produce severe, disabling motor fluctuations uncontrollable with oral medications. Advanced therapies are considered at this point, including deep brain stimulation or infusional therapies such as subcutaneous apomorphine or intraduodenal

levodopa gel infusions. Such therapies are generally reserved for patients who no longer improve with available oral and transdermal therapies and who lack cognitive or psychiatric dysfunction [4].

Apomorphine, intraduodenal levodopa, and deep brain stimulation can substantially improve motor fluctuations by decreasing daily "off" time and dyskinesias. Despite benefits that may continue several years after initiation, the underlying pathology progresses, and even patients with excellent response can experience the emergence of advancing disease with postural instability and falls, cognitive disturbance, autonomic dysfunction, and swallowing and speech dysfunction [4].

While large head-to-head studies comparing invasive procedures are lacking, deep brain stimulation has the highest level of supportive evidence from the largest number of randomized controlled trials. Before any decision is made to use invasive therapies, a multidisciplinary team should examine the patient and carefully weigh the relative risks and potential benefits of each therapy [106].

Pharmacotherapy Interventions

With apomorphine, the rapid onset of action makes it an effective intervention for "off" periods with use as a rescue injection. Apomorphine is also available as a continuous infusion treatment, suggested by clinical trials as effective in treating motor symptoms and some non-motor advanced PD symptoms [106].

With FDA approval in 2015, intestinal gel is the most recent formulation of levodopa/carbidopa to improve its blood concentration consistency and stability. In advanced PD, delayed and unpredictable spontaneous gastric emptying interferes with the passage of oral medication from the stomach to the small intestines for absorption and circulation to the brain. Levodopa/carbidopa intestinal gel (Duodopa) was developed to bypass this problem by delivering the drug directly to the proximal jejunum via a percutaneous endoscopic gastrojejunostomy tube connected to a portable infusion pump [126]. Compared to conventional immediate-release levodopa, levodopa/carbidopa intestinal gel has been found superior in improving motor fluctuations and quality-of-life scores. For example, 71 patients with advanced PD were randomized to levodopa/carbidopa intestinal gel plus oral placebo or oral levodopa/carbidopa plus placebo intestinal gel. After 12 weeks, the levodopa/carbidopa intestinal gel group showed a significant reduction in "off" time (-4.04 hours/day), versus the active oral/placebo gel group (+2.14 hours/day). This extent of improvement was also observed in "on" time without troublesome dyskinesia, and in "on" time without dyskinesia. Most side effects involved complications related to the percutaneous gastrojejunostomy therapy pump [127].

Deep Brain Stimulation Surgery

Surgical approaches are considered in patients with advanced PD when optimized medical treatment fails to control motor symptoms. Surgical interventions used in the past include ablative lesions in the nuclei of the basal ganglia or thalamotomy for tremor, and pallidotomy for levodopa-induced dyskinesias; however, approaches such as these incurred a high risk of permanent side effects. Although pallidotomy or thalamotomy remain options in carefully selected patients, deep brain stimulation is now the surgical treatment of choice for patients with advanced PD and symptoms refractory to medical management [2; 128]. This approach requires a small craniotomy for placement of electrodes connected to a pulse generator that is implanted in the chest wall. By modifying the frequency and amplitude of electrical stimuli, it is possible to improve motor symptoms and minimize side effects of brain stimulation over time. Unlike fixed ablative surgery, deep brain stimulation can be modified in response to changing symptoms as the disease progresses; adverse effects are usually reversible. The procedure can be performed in one or both hemispheres, depending on whether symptoms are unilateral or bilateral [95]. Although deep brain stimulation is able to reduce symptoms

of motor fluctuations, dyskinesia, and tremor, other refractory PD symptoms (e.g., cognitive impairment, gait instability, mood disorders, speech impairment, autonomic dysfunction) are unlikely to improve and may worsen as a result of this mode of therapy. Guidelines recommend that deep brain stimulation only be performed in experienced centers [2].

EVIDENCE-BASED PRACTICE RECOMMENDATION

According to the European Federation of Neurological Societies, deep brain stimulation of the subthalamic nucleus is effective against motor fluctuations and dyskinesia in later-stage PD, but because of the risk for adverse events, the procedure is only recommended for patients younger than 70 years of age without major psychiatric problems or cognitive decline.

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Level of Evidence: A (At least one convincing randomized, controlled clinical trial or at least two consistent, convincing prospective matched-group cohort studies)

For treatment of PD, deep brain stimulation targets the subthalamic nucleus of the internal capsule or the globus pallidus. Clinical trials of deep brain stimulation have reported a 40% to 60% reduction in the severity of motor symptoms and up to 50% reduction in medication use [128]. Short- and long-term studies have been conducted to assess the effectiveness of subthalamic nucleus stimulation for levodopa-refractory signs and symptoms. The overall improvement in activities of daily living and motor UPDRS scores averaged 50% compared to pre-surgery. Severity of levodopa-induced dyskinesias have been reduced by an average 69%. Surgical implantation of electrodes deep in the brain has a 1% to 6% risk of postoperative intracranial hemorrhage, infection, or stroke. Late-onset adverse events include migration or misplacement of the leads (5.1%), lead fractures (5%), and skin erosion (1.3%) [128; 129].

Factors contributing to deep brain stimulation outcome include clinical indications, patient selection, implantation accuracy, stimulation programming, and medication management. The symptoms and signs most frequently considered as possible late complications of deep brain stimulation include eyelid opening apraxia (1.8% to 30%), dysarthria/hypophonia (4% to 17%), gait disturbances (14%), postural instability (12.5%), weight gain (8.4%), and verbal fluency decline (14%) [95; 130]. As of 2016, more than 100,000 patients had undergone deep brain stimulation surgery for the treatment of PD and other movement disorders [131].

Timing

While deep brain stimulation was formerly offered only in late-phase disease (mean: 13 to 14 years post-diagnosis), several considerations have now moved the timing of surgery earlier [131]. Deep brain stimulation produces improvement in symptoms responsive to dopaminergic drugs, but in late-stage disease, symptom responsiveness to brain stimulation is less predictable and often unsatisfactory. Performing deep brain stimulation at advanced stages of illness can alleviate some motor dysfunction features but does not much benefit ongoing sense of well-being or functional status in relation to family, occupation, and social roles. In addition, older patients are more likely to develop surgical complications and/or worsening of axial motor functions.

The value of earlier deep brain stimulation surgery for PD was studied by comparing best medical treatment with deep brain stimulation of the subthalamic nucleus in 251 patients with early-stage motor fluctuation (mean: seven years post-diagnosis). Early and sustained improvement was found in quality of life for patients who received deep brain stimulation. Deep brain stimulation of the subthalamic nucleus has been proposed in patients less than four years after diagnosis without motor fluctuation, but this approach is less compelling, as it exposes patients to potentially dangerous side effects without improving motor function or quality of life. The long-term impact is also unclear [131].

Targeting

Several trials comparing subthalamic nucleus and globus pallidus pars intera stimulation have helped define relative advantages between these two targets. While motor benefits are comparable, other parameters show advantages with subthalamic nucleus for more severe on-off symptoms and cost-efficacy, and advantages with globus pallidus pars intera for dyskinesia suppression, long-term stability of effects, and cognitive symptoms [131].

Experimental and clinical observations suggest contribution from the pedunculopontine nucleus to the pathophysiology of gait and stability impairment. However, pedunculopontine nucleus stimulation remains investigational, with several unresolved issues [131].

Long-Term Impact

Early open-label studies reporting long-term (more than 10 years) outcomes in subthalamic nucleus stimulation consistently found durable benefits in motor fluctuation, dyskinesias, and the cardinal symptoms of PD (tremor, rigidity, and to a lesser extent, bradykinesia). A survival advantage was suggested when comparing eligible patients who chose deep brain stimulation versus those who continued medical treatment. However, subthalamic nucleus stimulation does not halt disease progression, and "long-term deep brain stimulation syndrome" with axial motor problems can emerge from long-term therapy. Reappraisal of current targets and investigation of new ones is ongoing [131].

In early 2025, the FDA approved an adaptive deep brain stimulation device that provides personalized therapy for patients with PD [132]. The Adaptive DBS Algorithm for Personalized Therapy in Parkinson's Disease (ADAPT-PD) trial was a prospective, single-blind, randomized crossover study (between two modes of adaptive deep brain stimulation), conducted across 10 centers in the United States, Europe, and Canada. It evaluated the safety and effectiveness of chronic dual- and single-threshold adaptive deep brain stimulation modes compared to continuous deep brain stimulation for eligible patients with PD receiving deep brain stimulation therapy. This study represents the largest and longest assessment of adaptive deep brain stimulation conducted in both clinical and home settings [132]. In adaptive deep brain stimulation, a machine learning system constantly measures changes in brain activity related to movement and adjusts the stimulation in real time, reducing the need for manual intervention when treating PD symptoms [133]. Emerging evidence suggests greater efficacy with fewer adverse effects during adaptive deep brain stimulation compared with conventional deep brain stimulation [134].

Alternative Surgical Approaches

Radiofrequency ablation and focused ultrasound are alternative modalities that can target the subthalamic nucleus and produce fixed brain lesions. The success rate of radiofrequency ablation of subthalamic nuclei for relief of parkinsonism is comparable to that of deep brain stimulation. Unfortunately, the benefit often dissipates after three years due to worsening PD or return of abnormal activity. Like deep brain stimulation, radiofrequency ablation requires craniotomy; it also has some risk of hemorrhage and stroke. Potentially irreversible adverse events include dyskinesia or hemiballismus, gait impairment, dysarthria, and loss of verbal fluency [128].

Ablation of certain deep brain centers can also be performed using focused ultrasound (FUS). Ablation with FUS has the advantage of producing lesions without the need for craniotomy; however, this modality has not yet proven to be safer than ablation methods that require craniotomy. Disadvantages of FUS for treatment of PD include persistent adverse effects (dysarthria, weakness, gait unsteadiness) and lack of the ability to modulate treatment over time [128].

MANAGEMENT OF NON-MOTOR SYMPTOMS

As discussed, patients frequently develop diverse non-motor symptoms and syndromes throughout the clinical course of PD. Most non-motor symptoms cluster into broader groups of abnormality: neuropsychiatric disorders, autonomic dysfunction, sleep disorders, and pain.

Neuropsychiatric Disorders

Psychosis in Parkinson Disease

Psychosis in PD is common and multifactorial in etiology. Up to 60% of patients with PD develop psychosis. Following its onset, PD psychosis remains a persistent, lifelong problem for most patients [135]. Pharmacologic management is challenging, in part because dopaminergic agents required for motor control can exacerbate psychotic symptoms, and antipsychotic agents can exacerbate motor symptoms [136]. The onset of psychosis in PD predicts a poor prognosis, including increased likelihood of nursing home placement and early mortality [137].

The early clinical manifestations of PD-associated psychosis differ from other psychotic disorders in that hallucinations are common and patients initially remain lucid and connected with reality. Visual hallucinations are the most prevalent form. Functional MRI performed on patients with PD who are experiencing visual hallucinations show several abnormalities: altered cortical visual processing; decreased occipital response and increased caudate and frontal cortical activation to visual stimuli; overactive visual association cortex; and decreased primary visual cortex activity [136].

Auditory, tactile, olfactory, and gustatory hallucinations do occur, though less commonly and usually in combination with visual hallucinations. Confusion states, delusions, paranoia, agitation, and delirium may also develop.

The stage of PD at which psychotic features emerge has some diagnostic import. In newly suspected or recently diagnosed (within three months) cases of PD, the appearance of psychotic symptoms suggests early-onset dementia with Lewy bodies, but could also indicate an alternative neuropsychiatric diagnosis, such as Alzheimer disease with extrapyramidal symptoms or underlying functional (psychiatric) psychosis. Differences in the initial presentation of PD-associated psychosis do not substantively change the management approach (with some caveats) [136].

Risk factors for PD-associated psychosis include cognitive impairment, dementia, advanced age, sleep disturbances, and disease duration/severity [138]. Psychosis is unrelated to total dose or duration of dopaminergic medication, and no differences have been found in the incidence rate among patients receiving levodopa versus those on dopamine agonists or anticholinergic drugs [139].

The association between sleep disturbance and PD psychosis is sufficiently robust to suggest REM sleep behavior disorder manifests from an evolving synucleinopathy in patients with PD-associated psychosis or dementia. Both factors may develop from a single epiphenomenon, such as neurodegeneration. Evidence also suggests contribution to PD psychosis from non-dopaminergic neurotransmitters, including serotoninergic or cholinergic systems [136].

Visual hallucinations require medication adjustment and possibly specific therapies if they are troublesome, threatening, or associated with behavioral change [4]. Triggering factors, such as infection, metabolic disorders, fluid/electrolyte imbalance, and sleep disorder, should be controlled. In addition, steps should be taken to reduce polypharmacy. Tricyclic antidepressants and anxiolytics/sedatives should be reduced or stopped. Antiparkinsonism drugs should also be reassessed. Anticholinergics and amantadine should be halted, while dopamine agonists and MAO-B and COMT inhibitors should be reduced or halted. The levodopa dose may be reduced [79; 140].

Unfortunately, most commonly used antipsychotic drugs have side effects that exacerbate PD. Consequently, atypical antipsychotics are often key in the management of PD-associated psychosis. Almost all antipsychotic drugs can exacerbate PD. Clozapine is the only antipsychotic with high-level evidence of efficacy; in some patients, it also improves motor function [141]. Clozapine is widely recommended as the first-line choice, but it is associated with potentially fatal agranulocytosis, which develops in 1% of patients and makes routine blood neutrophil counts mandatory. Less serious side effects include sedation, tachycardia, orthostatic hypotension, and sialorrhea. Low-dose clozapine (less than 50 mg) also has efficacy, with less frequent and more tolerable side effects and rare agranulocytosis [142; 143].

The AAN states quetiapine can be considered in the treatment of PD-associated psychosis [81]. However, some studies have found quetiapine no better than placebo in antipsychotic effect in this group of patients [144; 145]. Despite clozapine superiority, quetiapine is the most frequently used antipsychotic for PD-associated psychosis in the United States, due to better safety and despite inconsistent antipsychotic benefit [80; 139].

First-generation antipsychotics (e.g., haloperidol) should not be used. This drug class is a common cause of drug-induced parkinsonism, shows little to no psychotic symptom relief, and can worsen motor symptoms [136]. Other atypical antipsychotic agents (e.g., olanzapine, risperidone) can worsen parkinsonism and should not be used [80]. The FDA requires all atypical antipsychotics to carry black box warnings for increased risk of death in elderly patients with dementia [136].

Adding a cholinesterase inhibitor (e.g., rivastigmine, donepezil) is an option [79]. In patients requiring sedation for severe agitation, non-neuroleptics such as lorazepam should be considered over standard agents like haloperidol [80; 81].

Pimavanserin is an investigational drug with a novel mechanism of antipsychotic action as a selective serotonin 5-HT2A receptor inverse agonist. The activity of this drug does not block dopamine receptors and does not adversely affect PD. In clinical trials for the treatment of PD-associated psychosis, pimavanserin has shown efficacy and tolerability, including significant improvements in positive symptoms of psychoses, caregiver burden, and overall clinical improvement without worsening of motor function. No safety signals have emerged [106; 146].

Dementia

Dementia is the progressive decline in cognitive function (i.e., thinking, planning, organizing, problem solving) beyond what might be expected from normal aging. The dementia of PD takes two forms: an early, more rapidly progressive dementia characterized pathologically by an abundance of Lewy bodies within the brain (i.e., dementia with Lewy bodies), and a later onset, less rapid form characterized by neurodegenerative change and fewer Lewy bodies (i.e., PD dementia) [6]. The cognitive signs of dementia with Lewy bodies begin within one year of motor symptom onset, while the cognitive problems associated with PD dementia begin one or more years after motor symptom onset.

Dementia affects a substantial portion of people with PD and has virtually no effective treatment [6]. Cognitive impairment, autonomic dysfunction, and falls are all features of PD dementia that substantially affect function and quality of life and incompletely respond to medication manipulation [4].

In patients with typical PD dementia, there is an initial rapid loss of midbrain dopamine neurons followed by slow progression of Lewy body infiltration into the brain over decades. Dementia manifests later when Lewy bodies invade the neocortex. Patients diagnosed with PD after 70 years of age develop dementia earlier in the disease, show more alpha-synuclein-containing Lewy bodies throughout the brain, and often have additional age-related plaque pathology. In contrast, dementia with Lewy

bodies occurs with PD diagnosed at a younger age, is more rapidly progressive, and shows substantial amounts of Lewy bodies and Alzheimer-type pathologies infiltrating the brain. These data suggest that age at symptom onset and the extent and type of age-related, Alzheimer-type pathology influence pathologic progression in PD [6].

Management involves discontinuation of potential aggravators, including anticholinergics, amantadine, tricyclic antidepressants, tolterodine, oxybutynin, and benzodiazepines [79; 140]. A cholinesterase inhibitor, such as rivastigmine, donepezil, or galantamine, should be initiated. With idiosyncratic clinical response or side effects, an alternate agent may be tried. If cholinesterase inhibitors lack tolerability or efficacy, memantine should be added or substituted.

Depression

As many as 90% of patients with PD experience depression, which can appear in early and advanced disease. This neuropsychiatric problem has a major impact on both patients' and caregivers' quality of life. With many overlapping features between depression and PD before and during dopaminergic treatment (e.g., loss of facial expression, hypophonic speech, slowed movement, reduced appetite, sleep disorders), depression in PD often goes on unrecognized [95; 147].

Tricyclic antidepressants may be the best choice for depression treatment in PD, followed by selective serotonin or norepinephrine reuptake inhibitors (SSRIs/SNRIs) or dopaminergic agonist therapy. Cognitive-behavioral therapy also appears promising [148]. Most PD experts use an SSRI, SNRI, or tricyclic antidepressant and follow the patient closely for four to six weeks, adjusting as needed [106; 149].

The potential of antidepressants to worsen PD motor symptoms has been debated, but studies show no significant increase in risk of motor deterioration. A review of tricyclic antidepressant and SSRI/SNRI treatment of depression in PD concluded possible efficacy in reducing levodopa-induced dyskinesia [150]. There is a minor risk of impairing levodopa motor control, but this finding is inconsistent. The effect is usually minor when it happens and can be resolved by increasing levodopa dose [150]. Nortriptyline has no effect on dyskinesia or motor symptoms.

Tricyclic antidepressants and SSRIs/SNRIs are probably effective for depression [150]. The strongest evidence is for nortriptyline and paroxetine. SSRIs may not be the preferred drug class when rapid effect is needed, and quicker onset of therapeutic benefit is achieved with noradrenergic antidepressants. Tricyclic antidepressants and SSRIs/SNRIs are also beneficial in treating anxiety in patients with PD.

In other drug classes, the dopamine agonist pramipexole (up to 1 mg three times per day) significantly improved depression compared to placebo, an effect unrelated to motor improvement [106; 149]. Depression symptoms confined to "off" time may respond well to any treatment that reduces motor fluctuations and improves "on" time. Electroconvulsive therapy remains a potentially lifesaving treatment in major depression and has been used successfully in PD, but sufficient trials in PD depression do not exist [106; 149; 151].

Apathy

Apathy in non-demented and non-depressed patients with PD is not associated with dopamine transporter activity in the striatal sub-regions. It is more likely the result of extra-striatal lesions that accompany PD rather than striatal dopaminergic deficits [152].

No established treatment for apathy is available. Levodopa, selegiline, and antidepressants have been suggested as useful. In a small clinical trial, rivastigmine 9.5 mg/day transdermal significantly improved apathy symptoms beyond placebo response. There was also improvement in activities of daily living and caregiver burden, but not quality of life. Methylphenidate is probably effective in treating apathy and fatigue in later PD [150]. There is a lack of literature on the subject, many experts use a dopamine agonist for severe apathy, but with caution for impulsive behaviors [106; 153]. One meta-analysis that compared the efficacy of various treatment

modalities for PD found that pharmacotherapy was the most efficacious, followed by deep brain stimulation, exercise-based interventions, supplements, and placebo [154].

Impulse Control Disorders

Impulse control disorders and aberrant behaviors can develop during dopamine agonist treatment in PD and worsen patient and caregiver quality of life. Often, patients lack insight into the negative consequences of their behavior. Risk factors include male sex, younger age at onset, personality traits of high impulsivity and novelty seeking, and personal or family history of addictive disorders. In predisposed patients, overstimulation of mesocorticolimbic dopamine receptors by dopamine agonists leads to impulse control disorders and compulsive medication use. Impulse control disorders are more likely in early PD with normal-range medication dosing, while compulsive medication use is more commonly associated with fluctuations in advanced disease. Affected patients often lack noteworthy psychiatric histories and cognitive impairment, making identification difficult. Management requires reducing dopaminergic therapy, and psychosocial support is often necessary. SSRIs may help, while atypical antipsychotics have limited benefit. Prevention is based on the identification of at-risk individuals and active monitoring [155].

In a study of 203 patients with PD, the most common impulse control disorders were compulsive eating (14%), hypersexuality (10%), compulsive shopping (6%), and pathologic gambling (3%). Age younger than 68 years and exposure to dopamine agonists or MAO-B inhibitors were identified as risk factors for developing disorders of impulse control. Affected patients on dopamine agonists received a daily dose 60% higher than those without the disorders. Impulse control disorder symptoms showed a nonlinear dose-response relationship with dopamine agonists [156].

Autonomic Dysfunction

Constipation

In patients with PD, constipation may develop due to impaired gastrointestinal motility and medication side effects. Treatment is often behavioral, with a focus on increasing fluid ingestion, fiber intake, and physical activity. If additional treatment is necessary, polyethylene glycol solution, fiber supplements (e.g., psyllium, methylcellulose), and/or osmotic laxatives are recommended. Short-term irritant laxatives may help in selected patients [79; 140].

Dysphagia

Management of dysphagia requires optimization of motor control approaches. Speech therapy is indicated for assessment, swallowing advice, and further investigations, if needed. Videofluoroscopy may be conducted in selected cases to exclude silent aspiration. In severe cases, enteral feeding options (e.g., short-term nasogastric tube, percutaneous endoscopic gastrostomy) may be considered [79; 140].

Orthostatic Hypotension

Orthostatic hypotension is a symptomatic drop of 20 mm Hg systolic or 10 mm Hg diastolic blood pressure when rising to standing from sitting or lying down. Orthostatic hypotension is associated with lightheadedness, syncope, or nonspecific complaints including fatigue, unsteadiness, headache, neck tightness, or cognitive slowing. Because supine hypertension often accompanies orthostatic hypotension, the first step of treatment should be non-pharmacologic to avoid worsening supine hypertension. Patients should avoid, reduce, or eliminate large meals, alcohol, warm environments, volume depletion, diuretics, antihypertensive drugs, tricyclic antidepressants, nitrates, dopaminergic drugs (if possible), and alpha-blockers used for benign prostatic hypertrophy. Increasing salt intake may also help. Tilting the head of bed at night (30° to 40°) is recommended, as is exercise, as tolerated. Waist-high elastic stockings, abdominal compression bands, and counter-maneuvers (e.g., leg crossing, toe raising, thigh contraction) are effective prevention measures.

Midodrine has the greatest level of evidence in terms of pharmacotherapy. Fludrocortisone is also possibly effective, but it is important to monitor for side effects [79; 106; 140].

Urinary Dysfunction

Urinary incontinence in patients with PD is thought to result from hyper-reflexia caused by basal ganglia dysfunction. When symptoms appear suddenly, it is important to rule out urinary tract infection. If incontinence occurs mainly at night, fluid intake should be reduced after 6 p.m. and the head of the bed should be tilted up for sleep.

Night-time dopaminergic therapy should be optimized, and if necessary, an anticholinergic drug may be added. Guidelines recommend trospium chloride (10–20 mg two to three times per day) or tolterodine (2 mg twice per day) [79; 140]. However, trospium is less able to penetrate the blood-brain barrier, and cognition may worsen. Botulinum toxin type A injected in the detrusor muscle is also an option [79; 140].

Sexual Dysfunction

Sexual dysfunction is common in men and women with PD and is a complex problem from diverse etiologies, including motor dysfunction, medication side effects, mood disorders, and autonomic dysfunction manifesting in erectile dysfunction, reduced genital sensitivity and lubrication, and difficulty reaching orgasm [140].

Erectile dysfunction is widespread in PD and affects at least 50% to 75% of men with PD. Good evidence supports the use of sildenafil citrate, and similar drug class members, such as tadalafil and vardenafil, are also likely to be effective [95].

Sleep Disorders

Excessive Sleepiness

Excessive daytime somnolence and sudden sleep onset can originate from the disease process, medications, or other sleep disorders. Excessive daytime somnolence can result from dopaminergic medications—more commonly dopamine agonists than levodopa. Patients with these symptoms should be assessed for nocturnal sleep disturbances. Nocturnal sleep may be improved by reducing akinesia, tremor, and urinary frequency.

Sedative drugs should be reduced or discontinued. All dopaminergic drugs may induce daytime somnolence, so the dose of the current dopamine agonist may be reduced or the patient may switch to another dopamine agonist. Modafinil and/or other wake-promoting agents (e.g., methylphenidate) should be added [79; 140]. Patients with excessive daytime somnolence should be advised to stop driving.

Restless Legs Syndrome

Restless legs syndrome (RLS) is a movement disorder of the limbs whereby patients have a bothersome, irresistible urge to move the legs. RLS often interferes with sleep, leading to chronic sleep deprivation and stress. The prevalence of RLS was 12% in one study of patients with PD [157]. Drugs considered the most efficacious for RLS include levodopa, ropinirole, pramipexole, cabergoline, pergolide, and gabapentin; second-line options include rotigotine, bromocriptine, oxycodone, carbamazepine, valproic acid, and clonidine [158].

Insomnia

Insomnia in PD may be the result of mood disturbances, persistent tremor, night-time re-emergence of PD symptoms, nocturia, and reversal of sleep patterns [140]. Levodopa/carbidopa may contribute to insomnia while improving sleep-related motor symptoms. Melatonin may be effective in improving patients' perception of sleep quality [140].

REM Sleep Behavior Disorder

As discussed, REM sleep behavior disorder is a type of parasomnia characterized by the behavioral enactment of dreams during REM sleep. REM sleep behavior disorder is one of the most robust predictors of PD development and is very prevalent throughout the motor symptom phase of disease progression. Standard treatment is clonazepam or melatonin [59].

Pain

Among non-motor symptoms, 60% to 83% of patients with PD report pain of heterogeneous presentation and disabling effect on quality of life. Pain has received minimal attention in PD due to its association with the reappearance of motor symptoms and dystonic muscle contraction with dissipation of levodopa dose response. Pain also occurs as skeletal-muscle or neuropathic (peripheral or central) pain. Evidence suggests patients with PD have abnormal nociceptive processing in pain-free states, independent of parkinsonism motor symptom presence, that is unaffected by levodopa stimulation. Few therapeutic strategies for pain management in PD have been developed [159; 160].

A concern in using opioids to treat pain in patients with PD is potential exacerbation of constipation, a common, burdensome symptom of autonomic dysfunction. To possibly mitigate this issue, an oral formulation combining prolonged-release oxycodone with naloxone has been evaluated. In an eight-week trial, patients with PD-associated chronic pain received low-dose oxycodone/naloxone (5 mg/2.5 mg) twice daily. Of the 87.5% who completed the trial, significant pain reduction was achieved, no adjustment of dopaminergic therapy was required, no significant changes were observed in bowel function and constipation symptoms, no changes were observed in sleep symptoms, and improvements were recorded in clinician impression of therapeutic effect [161].

END-STAGE PARKINSON DISEASE

A little-studied area of PD has been symptom manifestation with approaching death and factors related to their severity and progression. The course of non-dopaminergic PD symptoms in relation to age and death was prospectively studied in 378 patients with PD over five years. Patients who died (11%) during follow-up had more severe non-dopaminergic symptoms. The progression of cognitive and axial symptoms accelerated in older patients, and the progression of axial, cognitive, and psychotic symptoms accelerated before death. Improving understanding of these factors will hopefully make a positive impact on end-of-life care [162].

End-of-Life Care

During end-stage PD, the focus of care is on palliation of symptoms and comfort. Patients with end-stage PD often exhibit cognitive impairment and progress to the point of requiring assistance with most activities. The best approach for patients with PD at the end of life is multidisciplinary palliative care with adequate physical, psychologic, and spiritual support. In earlier stages, the goal is to maintain patient independence for as long as possible; however, in end-stage PD, the focus is mainly on comfort and supportive care [163].

Non-motor symptoms such as depression, psychosis, urologic dysfunction, pain, and respiratory depression, become more common in end-stage PD. Over time, these symptoms may become the most prominent medical problem, leading to increasing decline in quality of life [163]. The first step in managing these symptoms may be reduction or discontinuing triggering pharmacotherapeutic agents, such as anticholinergics, MAO-B inhibitors, and opioids.

In the last days, the goals of the healthcare team are to ensure a peaceful death for the patient and to support the family during the dying process and throughout grief and mourning. The focus for the patient is management of symptoms and emotional and spiritual ease, and the focus for the family is education to prepare them for the dying process.

ADJUNCTIVE TREATMENT MODALITIES

A variety of nonpharmacologic, adjunctive interventions have been evaluated for management of PD. These include exercise programs and occupational, physical, and speech therapies. While clinical study design and control group issues have confounded the quality of evidence, clinical experience suggests that these approaches have value. The American Academy of Family Physicians recommends physical therapy, speech therapy, and occupational therapy be offered to patients with PD as part of an overall strategy for improving or maintaining function [2]. The specific benefits for allied health professional interventions to patients with PD include [164]:

Physical Therapy

- Gait re-education, improving balance and flexibility
- Increasing aerobic capacity
- Improving movement initiation
- Improving independent functioning, mobility, and daily activities
- Advising on safety in the home environment

Occupational Therapy

- Maintaining work and family roles, home care, and leisure activities
- Improving and maintaining transfers and mobility
- Improving self-care activities such as eating, drinking, washing, and dressing
- Addressing environmental issues to improve safety and motor function
- Cognitive assessment and appropriate intervention

Speech/Language Therapy

- Improving vocal loudness and pitch range (with programs such as Lee Silverman voice treatment)
- Teaching strategies to optimize speech intelligibility
- Ensuring effective means of communication maintained throughout the disease course, including use of assistive technologies
- Reviewing and managing safe and efficient swallowing to minimize risk of aspiration

For individuals with Parkinson disease, the American Physical Therapy Association recommends that physical therapists implement moderate- to high-intensity aerobic exercise to improve oxygen consumption, reduce motor disease severity and improve functional outcomes; and resistance training to reduce motor disease severity, and improve strength, power, nonmotor symptoms, functional outcomes, and quality of life.

(https://academic.oup.com/ptj/article/102/4/pzab302/6485202. Last accessed April 28, 2025.)

Strength of Recommendation/Level of Evidence: Strong/High

When capable of doing so, persons with PD should be encouraged to maintain a regular program of stretching and other physical exercise. In a randomized, controlled trial, tai chi training was seen to be more effective than resistance training or stretching in reducing balance impairments and falls in patients with mild-to-moderate PD [165]. The American Parkinson Disease Association has developed a free, web-based training program designed to teach fitness professionals how to best meet the unique needs of persons with PD [166]. Cognitive training is likely helpful for other patients. Patient and family member education is a key component of PD management, as is the use of support groups [104].

PRACTICE CONSIDERATIONS

Avoiding Inappropriate Medications

Many patients with PD require hospital admission for problems unrelated to motor pathology. Their medical care is typically received on non-neurology wards from staff unfamiliar with PD management, increasing the risk of inappropriate medications that exacerbate PD. Among inpatients with PD, 43.8% received inappropriate anti-dopaminergic medication at some point, primarily haloperidol and metoclopramide. The highest prevalence occurred in patients with PD on chronic antipsychotics [80].

Nausea and vomiting, common adverse effects of levodopa and dopamine agonists, may require antiemetic use. The centrally acting dopamine antagonists metoclopramide and prochlorperazine should not be used; the peripheral dopamine antagonist domperidone is the antiemetic of choice. The serotonin receptor antagonist ondansetron is another option [79; 80].

Healthcare professional education is suggested to improve the care of inpatients with PD. Pharmacists can play a key role in identifying inappropriate medications and in educating non-PD specialist professionals [80].

Safety Precautions with Dopaminergic Agents

With disease progression, patients with PD become more reliant on medication to maintain their ability to function. In addition to regular monitoring for drug-specific side effects, clinicians should be careful not to abruptly withdraw dopaminergic medication [95]. Patients and family should be educated on the importance of medication compliance and regular dosing so as to avoid rapid changes in efficacy. Special attention is required during periods of intercurrent illness, such as gastroenteritis or abdominal surgery, which may result in interruption of dosage or poor intestinal absorption. These measures help to avoid the potential development of acute akinesia or neuroleptic malignant syndrome. "Drug holidays" are not recommended due to the risk of developing neuroleptic malignant syndrome.

Considering the risks of sudden changes in dopaminergic medication, patients with PD admitted to hospitals or care facilities should receive their medication at the appropriate times or be allowed self-medication. Medication adjustment should be reserved for specialists in PD management [95].

Clinician-Patient Communication

In managing newly diagnosed patients, healthcare professionals should exhibit great sensitivity and understanding in describing disease symptoms and progression. As it progresses, PD complicates every aspect of daily living. Formerly routine tasks demand full attention and often cause frustration and anxiety. Over time, PD reduces work capacity, erodes earning potential, and may compromise social and family relationships. Disease progression leads to increased dependency and fosters feelings of being a burden to others. Increasing difficulties with writing and speaking, coupled with the loss of independence, often lead to social withdrawal, isolation, depression, frustration, and anger. Access to primary care, speech therapists, exercise programs, and emotional support is critical to managing the disease and living with dignity, and people living with PD require understanding and support as they struggle to maintain independence and adapt to living with a chronic condition [95].

Good communication is the foundation of care between patients with PD, their caregivers, and health professionals. Healthcare professionals' commitment to clear, compassionate communication can make a meaningful difference to their patients. When patients with PD understand healthcare professionals' recommendations, they can know what to expect and are better prepared to navigate the system, ask the right questions, and make the best personal choices [95].

Communicating effectively is more challenging when the patient's primary language differs from that of the practitioner. According to the U.S. Census Bureau, more than 68 million Americans speak a language other than English in the home, with approximately 26.2 million of them (8.4% of the population) speaking English less than "very well" [167]. It has been suggested that when patients are first evaluated, they should be asked what language is spoken at home and if they speak English "very well" [168]. In addition, patients should also be asked what language they prefer for their medical care information, as some patients prefer their native language even though they have said they can understand and discuss symptoms in English [168]. Many studies have demonstrated that the lack of an interpreter for patients with limited English proficiency compromises the quality of care and that the use of professional interpreters improves communication (errors and comprehension), utilization, clinical outcomes, and patient satisfaction with care [169; 170].

"Ad hoc" interpreters (untrained staff members, family members, friends) are often used instead of professional interpreters for a variety of reasons, including convenience and cost. However, the reliability and specificity of information obtained through ad hoc interpreters is less than with professional interpreters [171]. In addition, individuals with limited English language skills have indicated a preference for professional interpreters rather than family members [172]. A systematic review of the literature has shown that the use of professional interpreters facilitates a broader understanding and leads to better clinical care than the use of ad hoc interpreters [170].

Care decisions should be based upon best available evidence and provided by applicable professional standards. Issues to consider when communicating with people with PD and their caregivers include [95]:

- Style, manner, and frequency of communication that is compassionate and respectful
- Ease of access for those receiving information in a timely and appropriate manner throughout the progression of the disease
- Honesty and sensitivity in tailoring information to meet changing medical needs
- Encouragement of self-management to meet individual needs and preferences
- Inclusion of caregivers who are also impacted by PD and require information and support

Hospice

Traditionally, management of PD has focused on drug treatment and interdisciplinary care for a long-term, slowly progressive disorder. Palliative care specialists have not routinely been involved. Due to the long duration of the disease and the difficulty in predicting the time of death, patients with PD are frequently refused access to hospice and palliative care services [95].

INTERPROFESSIONAL PRACTICE AND COLLABORATION

PD is a chronic, progressive disease; its clinical expression unfolds gradually in stages, each stage with its own unique set of clinical issues. Medical management of PD is challenging and the clinical issues are multifaceted and complex for the patient, patient's family, and practitioner alike. As with most chronic diseases, the patient with PD often interacts with multiple different healthcare professionals regularly; in fact, interprofessional collaboration can be an effective way to reinforce management goals and improve patient compliance [173]. Evidence shows that an interprofessional team approach enhances effectiveness of clinical care and improves outcomes for patients with complex illness and diverse needs [174].

Interprofessional practice and collaboration (IPC) is a model of care provided by healthcare professionals with overlapping expertise and commitment to shared responsibility, mutual trust, and communication to achieve a common goal [174]. Increasingly, IPC has become a component of healthcare professionals' educational curricula; in the context of primary care and chronic disease management, IPC has been shown to foster patient-centered care and reduce healthcare costs [175; 176].

CONCLUSION

PD is an important, increasingly prevalent neurodegenerative disease of aging. Although the defining motor abnormalities are easy to recognize when the syndrome of parkinsonism is fully manifest, the onset and progression of clinical features are variable and often preceded or followed by non-motor symptoms of disease. The pathogenesis of PD remains vague, but the pathophysiology is clear enough to provide a rational basis for developing therapies to treat the motor dysfunction of PD and to lend hope for future development of more effective and innovative management strategies.

On average, patients with PD live for a decade or longer with their disease, which typically follows a progressively debilitating course. The likelihood of intercurrent complications is high, and at each stage there are new issues of chronic disease management that challenge healthcare providers and family alike. All involved should have a basic understanding of the clinical features of PD, the sources of suffering, principals of treatment, importance of compliance, and potential for drug-drug interactions and side effects. Best practice outcomes require the coordinated effort of well-informed primary care physician and nurse, subspecialist, pharmacist, and home health provider—an interprofessional healthcare team approach.

RESOURCES

National Institute of Neurological Disorders and Stroke
https://www.ninds.nih.gov/Disorders/All-Disorders/Parkinsons-Disease-Information-Page

American Parkinson Disease Association
https://www.apdaparkinson.org

Implicit Bias in Health Care

The role of implicit biases on healthcare outcomes has become a concern, as there is some evidence that implicit biases contribute to health disparities, professionals' attitudes toward and interactions with patients, quality of care, diagnoses, and treatment decisions. This may produce differences in help-seeking, diagnoses, and ultimately treatments and interventions. Implicit biases may also unwittingly produce professional behaviors, attitudes, and interactions that reduce patients' trust and comfort with their provider, leading to earlier termination of visits and/or reduced adherence and follow-up. Disadvantaged groups are marginalized in the healthcare system and vulnerable on multiple levels; health professionals' implicit biases can further exacerbate these existing disadvantages.

Interventions or strategies designed to reduce implicit bias may be categorized as change-based or control-based. Change-based interventions focus on reducing or changing cognitive associations underlying implicit biases. These interventions might include challenging stereotypes. Conversely, control-based interventions involve reducing the effects of the implicit bias on the individual's behaviors. These strategies include increasing awareness of biased thoughts and responses. The two types of interventions are not mutually exclusive and may be used synergistically.

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