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Diagnosis and Treatment of Parkinson Disease
A Review

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IMPORTANCE Parkinson disease is the most common form of parkinsonism, a group of neurological disorders with Parkinson disease–like movement problems such as rigidity, slowness, and tremor. More than 6 million individuals worldwide have Parkinson disease.

OBSERVATIONS Diagnosis of Parkinson disease is based on history and examination. History can include prodromal features (eg, rapid eye movement sleep behavior disorder, hyposmia, constipation), characteristic movement difficulty (eg, tremor, stiffness, slowness), and psychological or cognitive problems (eg, cognitive decline, depression, anxiety). Examination typically demonstrates bradykinesia with tremor, rigidity, or both. Dopamine transporter single-photon emission computed tomography can improve the accuracy of diagnosis when the presence of parkinsonism is uncertain. Parkinson disease has multiple disease variants with different prognoses. Individuals with a diffuse malignant subtype (9%-16% of individuals with Parkinson disease) have prominent early motor and nonmotor symptoms, poor response to medication, and faster disease progression. Individuals with mild motor-predominant Parkinson disease (49%-53% of individuals with Parkinson disease) have mild symptoms, a good response to dopaminergic medications (eg, carbidopa-levodopa, dopamine agonists), and slower disease progression. Other individuals have an intermediate subtype. For all patients with Parkinson disease, treatment is symptomatic, focused on improvement in motor (eg, tremor, rigidity, bradykinesia) and nonmotor (eg, constipation, cognition, mood, sleep) signs and symptoms. No disease-modifying pharmacologic treatments are available. Dopamine-based therapies typically help initial motor symptoms. Nonmotor symptoms require nondopaminergic approaches (eg, selective serotonin reuptake inhibitors for psychiatric symptoms, cholinesterase inhibitors for cognition). Rehabilitative therapy and exercise complement pharmacologic treatments. Individuals experiencing complications, such as worsening symptoms and functional impairment when a medication dose wears off ("off periods"), medication-resistant tremor, and dyskinesias, benefit from advanced treatments such as therapy with levodopa-carbidopa enteral suspension or deep brain stimulation. Palliative care is part of Parkinson disease management.

CONCLUSIONS AND RELEVANCE Parkinson disease is a heterogeneous disease with rapidly and slowly progressive forms. Treatment involves pharmacologic approaches (typically with levodopa preparations prescribed with or without other medications) and nonpharmacologic approaches (such as exercise and physical, occupational, and speech therapies). Approaches such as deep brain stimulation and treatment with levodopa-carbidopa enteral suspension can help individuals with medication-resistant tremor, worsening symptoms when the medication wears off, and dyskinesias.

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Neurological conditions are the leading source of disability worldwide, and the prevalence of Parkinson disease is increasing more rapidly than other neurological disorders.[1] Parkinson disease is the most common type of parkinsonism, a term reflecting a group of neurological disorders with Parkinson disease–like movement problems such as rigidity, slowness, and tremor. Less common parkinsonisms include other neurodegenerative diseases (eg, multiple system atrophy, progressive supranuclear palsy), drug-induced parkinsonism, and vascular parkinsonism. An estimated 6.1 million individuals globally had a Parkinson disease diagnosis in 2016, 2.4 times higher than in 1990.[1] This increasing prevalence was attributed to improved methods used to detect and diagnose Parkinson disease, greater awareness of the disease, aging populations, longer life expectancy, and possibly increased environmental exposures (eg, pesticides, solvents, metals) associated with industrialization.[1] It is estimated that approximately 930 000 people will be living with a Parkinson disease diagnosis in the United States in 2020.[2]

Parkinson disease is uncommon among individuals younger than 50 years and increases in prevalence with age, peaking between ages 85 and 89 years.[1] Parkinson disease is more common in men (1.4:1.0 male-to-female ratio).[1] Most cases of Parkinson disease are idiopathic, but there are known genetic and environmental contributions.[3] Pesticide, herbicide, and heavy metal exposures are linked to an increased risk of Parkinson disease in some epidemiologic studies, whereas smoking and caffeine use are associated with decreased risks.[3]

This review provides current information on diagnosis and treatment of Parkinson disease (**Box**).

Methods

A literature search for English-language systematic reviews and guidelines regarding the diagnosis and treatment of Parkinson disease was performed in PubMed, the Cochrane Database of Systematic Reviews, and the International Parkinson and Movement Disorder Society evidence-based medicine publications[4] on July 25, 2019 (updated on November 14, 2019). Search terms and results are reported in the eAppendix in the Supplement. PubMed was searched using the narrow diagnosis and therapy clinical queries[5] and the systematic review filter.[6] One author (M.J.A.) reviewed and selected abstracts that were relevant to Parkinson disease diagnosis and treatment. The second author (M.S.O.) reviewed the selected abstracts. When there was disagreement between abstracts selected, the authors reached consensus via discussion. Systematic reviews were included if they reported on treatment or diagnosis of Parkinson disease (rather than diagnosis of components of Parkinson disease [eg, depression]). Reviews performed in the last 5 years were considered higher priority for inclusion. When multiple reviews covered the same topic, the authors discussed and reached consensus on which review to include, based on relevance and recency of data. Only diagnosis and treatment approaches currently available in clinical practice were included. When identified reviews did not cover relevant topics, articles were selected based on informal consensus of relevance and rigor.

Box. Commonly Asked Questions About Parkinson Disease

Are There Diagnostic Tests for Parkinson Disease?
Diagnosis of Parkinson disease is based on history and physical examination. Dopamine transporter single-photon emission computed tomography scans are approved by the US Food and Drug Administration for use when a diagnosis is unclear and the differential diagnosis includes both essential tremor and Parkinson disease. Dopamine transporter single-photon emission computed tomography scans show decreased putaminal tracer uptake in Parkinson disease and other parkinsonian syndromes, but they show normal uptake in essential tremor. Magnetic resonance imaging (MRI) may help differentiate Parkinson disease from other parkinsonisms, such as vascular parkinsonism (in which MRI shows vascular changes) and atypical parkinsonisms including multiple system atrophy (in which MRI can show features such as the "hot cross bun" sign) and progressive supranuclear palsy (in which MRI can show an abnormal magnetic resonance parkinsonism index).

What Medication Should Be Started First for Parkinson Disease?
There are many therapeutic options for treating Parkinson disease, including therapy with carbidopa-levodopa, monoamine oxidase-B inhibitors, and dopamine agonists. If individuals report disability from Parkinson disease symptoms such as having difficulty typing, which affects their job, therapy with carbidopa-levodopa typically provides the greatest benefit.

How Soon Should Rehabilitative Therapies Be Prescribed After a Patient Is Diagnosed With Parkinson Disease?
At the time of diagnosis, an appropriate exercise regimen can be prescribed based on the patient's symptoms. Rehabilitative therapies should be continued throughout the disease course.

How Quickly Does Parkinson Disease Progress?
Progression of Parkinson disease varies. There are slower- and faster- progressing forms of Parkinson disease. A patient's symptoms, rate of symptom progression, and medication response are all associated with the rate of disease progression. For example, individuals with early cognitive impairment, orthostatic hypotension at presentation, and a poor response to levodopa tend to have more rapid Parkinson disease progression.

When Should Deep Brain Stimulation or Other Surgical Approaches Be Considered as Therapy?
Deep brain stimulation and other surgical approaches are typically considered when individuals with Parkinson disease experience either the "wearing off" phenomenon or dyskinesias, and these experiences do not respond to medication adjustments. Wearing off is defined by recurrence of Parkinson disease symptoms and functional disability that occurs during the time period immediately before the next medication dose is due. Dyskinesias are involuntary movements often occurring at peak medication concentrations.

Do People Die From Parkinson Disease?
Most people with Parkinson disease die from the same causes as age-matched individuals without Parkinson disease. However, if a person lives with Parkinson disease for years, they may die from Parkinson disease–related causes, such as aspiration pneumonia or complications from a fall.

Discussion and Observations

A total of 147 published reviews were identified from the PubMed (n = 75) and Cochrane database (n = 72) searches, 26 of which

Table 2. Motor and Nonmotor Symptoms and Signs of Parkinson Disease

Symptom or Sign	Definition or Key Elements
Motor	
Bradykinesia[a]	Slowness and progressively smaller movements (hypokinesia)as an individual repeats a task (eg, tapping index finger and thumb, opening and closing fist) multiple times in a row
Rigidity[a]	Involuntary, velocity-independent resistance to passive movement of a joint (eg, elbow, wrist) by an examiner, with or without a cogwheel phenomenon
Rest tremor[a]	A 4- to 6-Hz tremor in a fully resting limb, which temporarily disappears when the limb is held outstretched and then returns (reemergent tremor) and is not present during movement
Postural instability	Balance impairment affecting a person's ability to change or maintain postures such as walking or standing; typically a late Parkinson disease feature
Nonmotor	
Olfactory loss	Decreased or absent sense of smell (hyposmia)
Sleep dysfunction	Symptoms of rapid eye movement sleep behavior disorder, daytime sleepiness, sleep-maintenance insomnia
Autonomic dysfunction	Constipation, delayed gastric emptying, urinary urgency and frequency, erectile dysfunction, orthostatic hypotension, blood pressure variability
Psychiatric disturbances	Depression, anxiety, apathy, psychosis
Cognitive impairment	Mild cognitive impairment or dementia, often initially affecting attention, executive, and visuospatial functions
Other	Fatigue, hypophonia (softening of the voice), sialorrhea, trouble swallowing

[a] Indicates a primary feature.

were identified as potentially relevant for inclusion. Two additional reviews from the International Parkinson and Movement Disorder Society evidence-based medicine publications were included.

Pathophysiology

Parkinson disease is characterized by death of dopaminergic neurons in the substantia nigra. The pathologic hallmark of Parkinson disease is the Lewy body, a neuronal inclusion consisting largely of α-synuclein protein aggregations. The most widely cited model to explain neuropathological progression of Parkinson disease is the Braak hypothesis.[7] This model suggests that Parkinson disease starts (stages 1 and 2) in the medulla and the olfactory bulb. This early pathology is associated with symptoms occurring prior to the movement disorder onset, such as rapid eye movement sleep behavior disorder (in which individuals lose normal rapid eye movement sleep paralysis and physically act out their dreams while sleeping) and decreased smell. In stages 3 and 4, pathology progresses to the substantia nigra pars compacta and other midbrain and basal forebrain structures. Pathology in these areas is associated with classic Parkinson disease motor symptoms. Parkinson disease is typically diagnosed at this stage. In advanced Parkinson disease, the pathology progresses to the cerebral cortices with onset of cognitive impairment and hallucinations.[7]

Parkinson disease protein aggregations are associated with death of dopamine-producing cells. Treatments supplementing dopamine are the mainstay of Parkinson disease treatment. However, other neurotransmitter systems are also dysfunctional in Parkinson disease, including serotonin,[8-11] acetylcholine,[9,10,12] and norepinephrine systems (Table 1).[10] This explains why some Parkinson disease symptoms are refractory to dopamine-based medications. Some novel therapeutic approaches target these alternative neurotransmitter systems.

Clinical Presentation

Parkinson disease causes motor and nonmotor symptoms (**Table 2**). Motor symptoms consist of movement and physical tasks: tremor, stiffness, slowness, and imbalance. Nonmotor (nonmovement) symptoms affect many organ systems, such as gastrointenstinal and genitourinary systems, and are heterogeneous. Patients may not proactively volunteer nonmotor symptoms because they are embarrassed, appointment time is focused on motor symptoms, or they are unaware that the symptoms could be Parkinson disease related.[13]

Individuals diagnosed with Parkinson disease typically have gradual development of nonmotor symptoms for years before movement symptoms begin, but often they will not mention these symptoms unless specifically queried. These prodromal nonmotor features include rapid eye movement sleep behavior disorder, loss of smell, constipation, urinary dysfunction, orthostatic hypotension, excessive daytime sleepiness, and depression.[14] These symptoms are not Parkinson disease specific, but when they co-occur, the risk of a subsequent Parkinson disease diagnosis is greater.[14] Rapid eye movement sleep behavior disorder, particularly if identified on polysomnography, is strongly associated with increased risk of a subsequent diagnosis of Parkinson disease.[14] More than 90% of individuals with idiopathic rapid eye movement sleep behavior disorder eventually develop a synuclein-related neurodegenerative disease, usually Parkinson disease or a related condition (dementia with Lewy bodies, multiple system atrophy).[15] An estimated 30% to 50% of individuals with Parkinson disease have rapid eye movement sleep behavior disorder.[16]

Prodromal symptoms are associated with early Parkinson disease brainstem pathology. Once neuropathological progression results in loss of approximately half of cells in the caudal substantia nigra, motor signs and symptoms of Parkinson disease appear,[17]

Table 1. Neurotransmitters and Pharmacologic Agents Relating to Parkinson Disease Symptoms
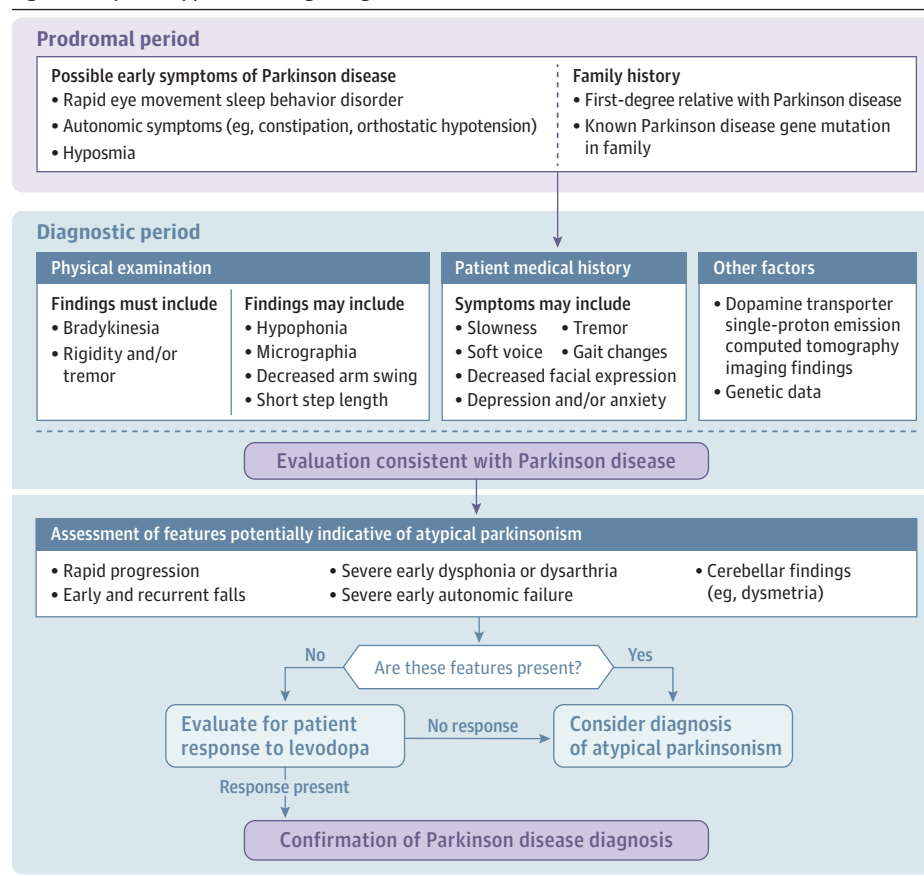
| Symptom or Sign | Neurotransmitters and Drugs Influencing the Neurotransmitter | | | | |
	Dopamine	Serotonin	Norepinephrine	Acetylcholine	Other
Motor impairment (eg, bradykinesia, rigidity, tremor, gait disturbance)	Levodopa preparations, dopamine agonists (eg, pramipexole, ropinirole), monoamine oxidase-B inhibitors (eg, rasagiline, selegiline), catechol-O-methyl transferase inhibitors (eg, entacapone)			Anticholinergic agents for tremor (eg, trihexyphenidyl)[a]; cholinesterase inhibitors for gait (eg, rivastigmine)[a,b]	Amantadine[c]
Cognitve impairment	Monoamine oxidase-B inhibitors[a,b]			Cholinesterase inhibitors	
Psychosis	Quetiapine, clozapine[a]	Pimavanserin		Cholinesterase inhibitors[a,b]	
Depression, anxiety	Dopamine agonists[a]	Selective serotonin reuptake inhibitors, selective serotonin and norepinephrine reuptake inhibitors, tricyclic antidepressants	Selective serotonin and norepinephrine reuptake inhibitors, tricyclic antidepressants	Tricyclic antidepressants	

[a] Indicates US Food and Drug Administration approved for another use but off-label use for the sign or symptom in this row.

[b] Studied for this use with insufficient evidence to date to support routine use.

[c] Amantadine may affect multiple neurotransmitter systems including dopamine and glutamate.

Figure 1. Proposed Approach to Diagnosing Parkinson Disease

Prodromal period

Possible early symptoms of Parkinson disease
• Rapid eye movement sleep behavior disorder
• Autonomic symptoms (eg, constipation, orthostatic hypotension)
• Hyposmia

Family history
• First-degree relative with Parkinson disease
• Known Parkinson disease gene mutation in family

Diagnostic period

Physical examination

Findings must include
• Bradykinesia
• Rigidity and/or tremor

Findings may include
• Hypophonia
• Micrographia
• Decreased arm swing
• Short step length

Patient medical history

Symptoms may include
• Slowness   • Tremor
• Soft voice   • Gait changes
• Decreased facial expression
• Depression and/or anxiety

Other factors
• Dopamine transporter single-proton emission computed tomography imaging findings
• Genetic data

Evaluation consistent with Parkinson disease

Assessment of features potentially indicative of atypical parkinsonism
• Rapid progression
• Early and recurrent falls
• Severe early dysphonia or dysarthria
• Severe early autonomic failure
• Cerebellar findings (eg, dysmetria)

Are these features present?
No → **Evaluate for patient response to levodopa**
Yes → **Consider diagnosis of atypical parkinsonism**
No response →
Response present → **Confirmation of Parkinson disease diagnosis**

Diagnosis of Parkinson disease requires obtaining history regarding prodromal symptoms, family history, and current concerns. Examination must show the core features of bradykinesia and rigidity and/or tremor, but other examination features such as the presence of orthostatic hypotension can also be helpful. Once history and physical examination features of parkinsonism are confirmed, the clinician excludes features potentially indicative of atypical parkinsonism ("red-flag symptoms") and assesses the patient response to levodopa (or potentially other dopaminergic medications) to confirm Parkinson disease.

and individuals present with personal or family concerns regarding gradual onset of resting tremors, slowness, and/or generalized (not joint-specific) stiffness. Approximately 20% of individuals with Parkinson disease do not present with resting tremors.[8,18]

Assessment and Diagnosis

A Parkinson disease diagnosis is primarily based on history and physical examination (**Figure 1**). History should assess motor and nonmotor symptoms (Table 2). Family history of a first-degree relative

Table 3. Settings in Which Parkinson Disease Cannot Be Confirmed[a]

Patient Characteristic	Possible Alternative Diagnosis
Use of dopamine-blocking medication (eg, metoclopramide, prochlorperazine, promethazine, antipsychotic medications)	Drug-induced parkinsonism
Symptoms limited to the legs for more than 3 years	Vascular parkinsonism
Trouble looking down during the examination process	Progressive supranuclear palsy
Cerebellar findings	Multiple system atrophy

[a] In some settings, Parkinson disease cannot be confirmed if medications may be responsible for the the patient's signs and symptoms or if additional findings suggest an alternative diagnosis. For additional information, see Postuma et al.[19]

with Parkinson disease increases the likelihood of a diagnosis of Parkinson disease.[14]

Clinical diagnostic criteria for Parkinson disease require an individual to have parkinsonism, defined as bradykinesia with rest tremor, rigidity, or both[19] (Table 2). For clinically established Parkinson disease (ie, certainty based on clinical presentation but not pathologic confirmation), individuals also need to meet at least 2 of 4 supportive criteria: (1) rest tremor, (2) a dramatic improvement with dopaminergic therapy (eg, carbidopa-levodopa), (3) the presence of levodopa-induced dyskinesias, or (4) the presence of either olfactory loss or cardiac sympathetic denervation on iodine-123-meta-iodobenzylguanidine myocardial scintigraphy (an imaging test that assesses cardiac norepinephrine uptake, which depends on intact postganglionic sympathetic neuron function [decreased in Parkinson disease]).[19] Dyskinesias are involuntary dance-like choreoathetoid movements that occur with dopaminergic therapy. Dyskinesias usually occur years after Parkinson disease medications are initiated and have limited benefit for diagnosis at symptom onset.[20] In some settings, Parkinson disease cannot be confirmed if medications may be responsible for the patient's signs and symptoms or if additional findings suggest an alternative diagnosis (Table 3).[19]

Dopamine transporter single-photon emission computed tomography (DaT SPECT) identifies the presynaptic dopamine neuronal dysfunction present in Parkinson disease and other neurodegenerative parkinsonisms by demonstrating reduced uptake of a radioactive tracer that binds to dopamine transporters in the basal ganglia. DaT SPECT is highly accurate (98%-100% sensitivity and specificity) in detecting nigrostriatal cell loss in individuals with parkinsonism.[21] In 2011, the US Food and Drug Administration (FDA) approved DaT SPECT imaging for distinguishing Parkinson disease from essential tremor, but these scans are not routinely needed. DaT scans are generally useful only when the presence of parkinsonism is uncertain on examination. If a patient has unequivocal parkinsonism, the scans are typically positive and add little to the diagnostic assessment.[22,23] They cannot differentiate between Parkinson disease and other parkinsonisms (eg, multiple system atrophy, progressive supranuclear palsy) that also involve dopamine transporter dysfunction.

Magnetic resonance imaging (MRI) is not typically helpful for diagnosing Parkinson disease. Specific MRI findings (eg, the magnetic resonance parkinsonism index, which is abnormal in progressive supranuclear palsy) can help differentiate Parkinson disease from other parkinsonisms; advanced techniques have future diagnostic and prognostic potential.[24,25] MRI findings of extensive cerebrovascular disease or basal ganglia lacunes can suggest a potential vascular contribution. Largely used outside the United States, iodine-123-meta-iodobenzylguanidine myocardial scintig-

raphy aids in evaluating for sympathetic nerve dysfunction, which commonly occurs as part of parkinsonisms.[26]

Parkinson Disease Subtypes

Increasing evidence suggests that Parkinson disease consists of heterogeneous subtypes. Subtypes have implications for diagnosis, prognosis, and expected treatment response. Initial subtyping focused on motor features,[27,28] but recent categorizations use data-driven clustering approaches.[27] These approaches suggest that subtypes are defined by motor and nonmotor features.[27,29-31] One approach to subtyping consists of 3 groups:

Mild motor predominant: younger age at onset, mild motor and nonmotor symptoms, slow progression, good medication response.[29,32]

Intermediate: intermediate age at onset and symptomatology, moderate-to-good response to medications.[29,32]

Diffuse malignant: baseline motor symptoms accompanied by rapid eye movement sleep behavior disorder, mild cognitive impairment, orthostatic hypotension, worse levodopa response, more prominent dopaminergic dysfunction on DaT SPECT, more atrophy in specific MRI voxels, low amyloid-β and amyloid-β/t-tau ratio in the cerebrospinal fluid, and rapid progression.[29,32]

When individuals are categorized this way, the mild motor-predominant form is the most common (49%-53%), followed by the intermediate form (35%-39%). The diffuse malignant form is least common (9%-16%).[29,32] Whether this subtyping is the best approach remains unclear, and individuals with Parkinson disease are not routinely categorized in clinical practice. However, clinicians should recognize that there are diverse presentations of Parkinson disease, and these categories may be useful for counseling individuals with Parkinson disease regarding variability in symptoms, medication responsiveness, and progression (Figure 2).
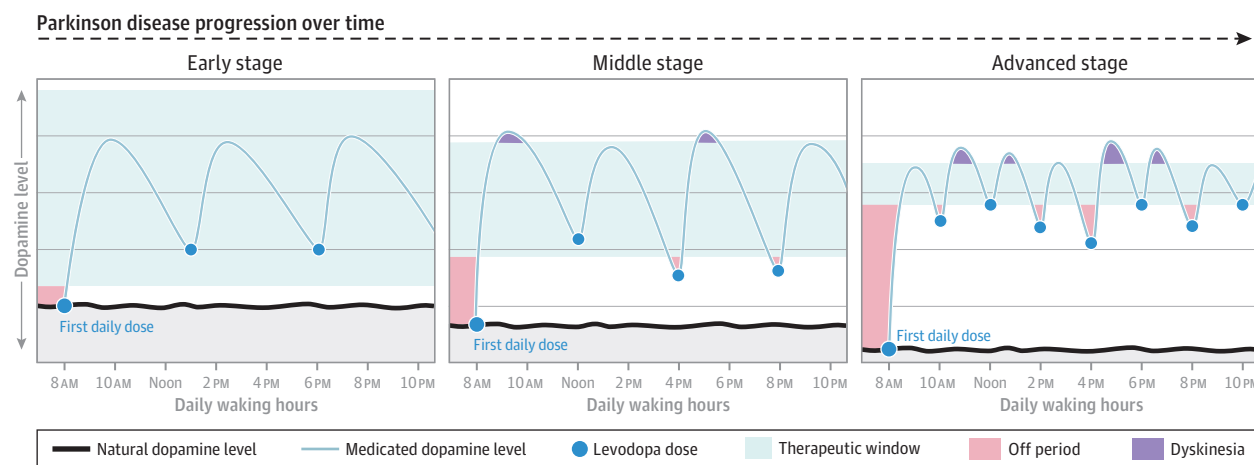
Prognosis

Parkinson disease involves progressive neurodegeneration and increasing symptom burden. A meta-analysis of postmortem studies found that people typically lived 6.9 to 14.3 years after a diagnosis of Parkinson disease, however, there was substantial heterogeneity.[33] In the Sydney multicenter study, 36 of 136 participants (26%) diagnosed with Parkinson disease in 1984-1987 lived for at least 20 years.[34] Parkinson disease–related deaths increase with age.[1] Causes of death on death certificates of individuals with Parkinson disease are similar to causes in non-Parkinson disease cohorts, with death often occurring before advanced disease stage.[35] When individuals die of Parkinson disease–related symptoms, aspiration pneumonia is the most common cause.[36]

Figure 2. Proposed Parkinson Disease Subtypes

Parkinson Disease Subtype and Estimated Frequency	Disease Presentation	Response of Motor Symptoms to Dopaminergic Medication	Disease Progression
Mild motor predominant 49%-53%	• Young at onset • Mild motor symptoms	Good	Slow
Intermediate 35%-39%	• Intermediate age at onset • Moderate motor symptoms • Moderate nonmotor symptoms	Moderate to good	Moderate
Diffuse malignant 9%-16%	• Variable age at onset • Rapid eye movement sleep behavior disorder • Mild cognitive impairment • Orthostatic hypotension • Severe motor symptoms • Early gait problems	Resistant	Rapid

Parkinson disease has multiple subtypes stratified according to presentation, medication responsiveness, and progression. While the optimal approach remains under investigation, recent studies divide Parkinson disease into 3 categories: mild motor-predominant, intermediate, and diffuse-malignant forms.

Figure 3. The Interaction Between Medication Dosing, Wearing Off, and Dyskinesias Over Time

Parkinson disease progression over time

Early stage | Middle stage | Advanced stage

Natural dopamine level — Medicated dopamine level — Levodopa dose — Therapeutic window — Off period — Dyskinesia

Levodopa is typically dosed 3 times daily to start (around meal times), which provides adequate dopamine concentrations across daytime hours. As Parkinson disease progresses, higher and more frequent levodopa doses are required due to decreasing short- and long-duration responses to dopaminergic medication and an inability to store excess dopamine.

Dyskinesias can also develop, typically occurring at the time of maximal levodopa concentrations in the brain (peak dose). The therapeutic window when dopaminergic medications are helping motor symptoms ("on" time) without dyskinesias narrows over the progression of the disease.

Expected progression is variable. In a clinical-pathologic assessment of the 3 proposed subtypes, the diffuse malignant group had a mean (SD) time from diagnosis to first milestone (regular falls, wheelchair dependence, dementia, or residential/nursing home placement) of 3.5 (3.2) years, compared with 8.2 (5.3) years for the intermediate form and 14.3 (5.7) years for the mild motor-predominant form. Mean (SD) survival after diagnosis was 8.1 (5.4) years for the diffuse malignant group, 13.2 (6.7) years for the intermediate subtype, and 20.2 (7.8) years for the mild motor-predominant form.[32]

Individuals with malignant Parkinson disease have earlier and more severe symptoms, poor response to medications, and rapid progression.[29,32] However, most individuals with Parkinson disease have moderate to good dopaminergic medication response[29,32] but experience increased Parkinson disease symptoms when a medication dose wears off ("off" periods)

and dyskinesias over time. Off periods improve with the next medication dose (Figure 3) and they can occur within 2 years of starting levodopa, but their prevalence increases over time.[37] Off periods are associated with functional disability and can include motor and nonmotor symptoms.[37] An estimated 40% of individuals with Parkinson disease experience dyskinesias after 4 to 6 years of levodopa treatment, typically at times of high levodopa concentrations (Figure 3).[20] Dyskinesia onset is associated with longer duration of Parkinson disease and higher levodopa doses rather than the length of time a patient has taken levodopa.[38,39] Although dyskinesia is severe in only 3% of individuals with Parkinson disease treated with levodopa (11% of individuals with dyskinesia), the presence of dyskinesia prompts medication changes in more than 60% of individuals with this feature,[40] presumably secondary to embarrassment or interference with activities.

Select nonmotor symptoms (hyposmia, rapid eye movement sleep behavior disorder, depression, constipation) start in prodromal Parkinson disease, but the nonmotor symptom burden increases as Parkinson disease progresses.[10] Sensory symptoms include hyposmia (occurring in >90% of individuals with Parkinson disease), visual disturbances (22%-78%), and somatosensory dysfunction and pain (30%-85%).[10] Autonomic symptoms include constipation, orthostatic hypotension, and urinary dysfunction (eg, nocturia, urgency, frequency), all increasing in frequency with disease progression.[10] Neuropsychiatric symptoms include anxiety (60%), apathy (60%), and depression (35%).[10] Psychosis occurs in approximately 40% of individuals with Parkinson disease, usually in later stages.[10] Mild cognitive impairment can be present at Parkinson disease diagnosis or develop over time. The cumulative probability of dementia in Parkinson disease is 46% at 10 years[41]; among Parkinson disease patients with 20-year survival, 83% have dementia.[34] Parkinson disease dementia is one form of Lewy body dementia, a term that also includes dementia with Lewy bodies.

Advanced Parkinson disease is characterized by severe off periods, dyskinesias, cognitive impairment, apathy, hallucinations, excessive daytime sleepiness, autonomic dysfunction, moderate to severe dysphagia, moderate to severe dysarthria, postural and balance impairments, freezing of gait (sudden brief episodes in which a person is unable to move their feet forward despite trying to walk), recurrent falls, and disability requiring help for activities of daily living (ADLs).[42] Advanced symptoms generally have little to no benefit from Parkinson disease therapies because the changes causing the dysfunction are outside the dopaminergic pathways.[42]

Treatment

Treatment for Motor Symptoms

Pharmacologic treatments for Parkinson disease motor symptoms are primarily dopamine based (Table 1). Levodopa preparations, dopamine agonists, and monoamine oxidase-B (MAO-B) inhibitors are useful initial therapies (**Figure 4**, **Figure 5**).[43] For young individuals with prominent tremor, anticholinergic agents (eg, trihexyphenidyl) are useful, but caution is required because of the potential for adverse events, particularly relating to cognition.[43]

Although previously many physicians avoided levodopa for early Parkinson disease treatment, recent research does not support this approach.[44] One trial (PD MED)[45] found that individuals randomly assigned to begin treatment with levodopa (n = 528) had small but persistent mobility benefits 7 years later (1.8-point improvement [95% CI, 0.5-3.0; P = .005] in average score on the Parkinson Disease Questionnaire-39 mobility subscale [10-items; 0- to 40-point range]) compared with individuals treated initially with dopamine agonists (n = 632) or MAO-B inhibitors (n = 460).[45] Performance of ADLs was also better in the levodopa initiation group over 7 years (1.9-point improvement [95% CI, 0.7-3.0; P = .002] in average score on the Parkinson Disease Questionnaire-39 ADL subscale [6-items, 0- to 24-point range]).[45] Participants in whom levodopa was initiated first were more likely to develop dyskinesias (hazard ratio, 1.52 [95% CI, 1.16-2.00]; P = .003), but there was no difference in motor fluctuations between groups (hazard ratio, 1.11 [95% CI, 0.90-1.37]; P = .3).

There was a greater likelihood of discontinuing the study medication among participants randomized to begin MAO-B inhibitors (72%) or dopamine agonists (50%) than among participants randomized to receive levodopa (7%; P <.001), usually due to adverse events.[45]

More than 40% of individuals treated with oral dopamine agonists (ropinirole, pramipexole) experience impulse control disorders (eg, gambling, compulsive spending, abnormal sexual and eating behaviors, compulsive medication use, hobbyism).[46] Individuals who discontinue use of dopamine agonists, often due to impulse control disorders, experience withdrawal symptoms (eg, anxiety, panic attacks, irritability, diaphoresis, pain, drug cravings) 15% to 20% of the time. Due to this, sometimes the dopamine agonist cannot be discontinued despite serious associated adverse events such as impulse control disorders.[47,48]

Selecting the optimal strategy for starting treatment of Parkinson disease requires shared decision making with the patient to consider benefits and risks. Levodopa use results in more functional improvements but has increased dyskinesia risks, particularly with higher doses. Severe dyskinesias are uncommon.[40] MAO-B inhibitors and dopamine agonists are associated with less robust symptom relief but lower dyskinesia risk; dopamine agonists are associated with a higher overall risk of adverse events.[45] Ultimately, most individuals with Parkinson disease use medications from multiple classes to attain complementary benefits while limiting high medication doses and dose-related adverse events.

Over time, individuals with Parkinson disease commonly require more frequent levodopa doses (eg, every 2-3 hours) in addition to higher doses (Figure 3). This phenomenon is not due to medication tolerance or loss of efficacy of levodopa. As Parkinson disease progresses, individuals lose their long-duration response to dopaminergic medication, and their short-duration response decreases due to disease-related pathophysiologic changes in the brain.[37] The brain also loses the ability to store extra dopamine (whether produced internally or provided through medication) for later use.[37]

Various medications are useful adjuncts to levodopa (Figure 4). MAO-B inhibitors and dopamine agonists are dosed 1 to 3 times daily (depending on drug, formulation) throughout the disease course, unlike levodopa, which requires more frequent dosing over time. Catechol-O-methyltransferase inhibitors and MAO-B inhibitors block enzymes that degrade dopamine, prolonging the benefits of levodopa. For individuals with severe off periods and delayed onset with subsequent dosing, subcutaneous apomorphine injections[49] and inhaled levodopa[50] can be used to achieve a faster medication response. Subcutaneous apomorphine is self-administered via an injection pen, and inhaled levodopa consists of an encapsulated powder administered orally via an inhaler. Each of these therapies can be used up to 5 times daily. Intermittent and continuous apomorphine infusions are available outside the United States.[49] Dyskinesias are treated by reducing dopaminergic medications or adding amantadine.[43] Immediate-release amantadine is used off label for dyskinesias,[43] with 2 extended-release preparations approved by the FDA.[51,52]

Effective exercise interventions for Parkinson disease include gait and balance training,[53] progressive resistance training,[54]

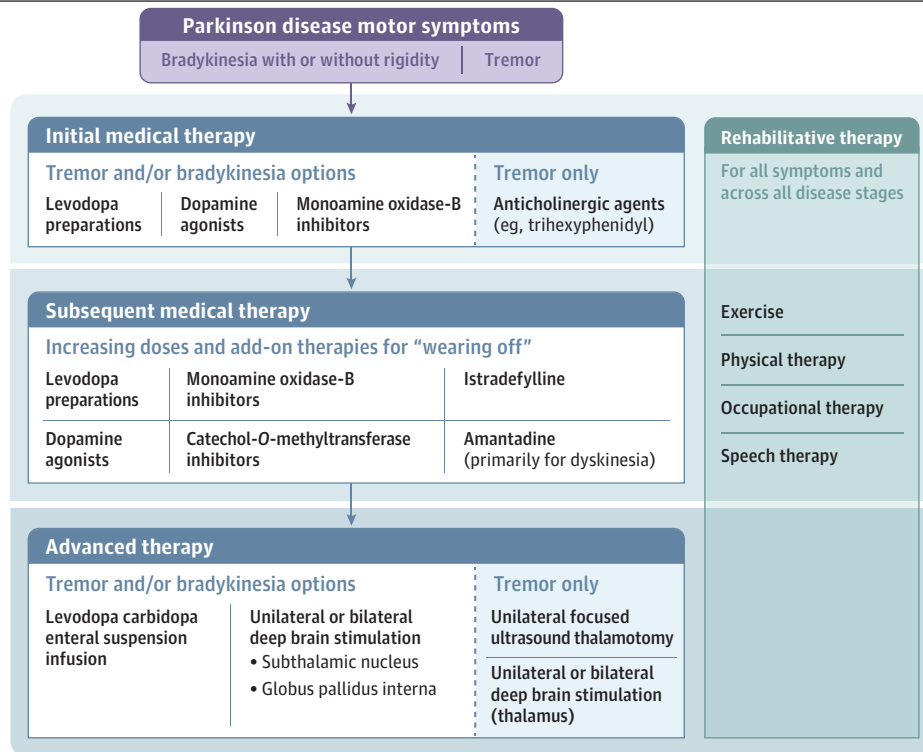Figure 4. Pharmacologic Agents Used for Motor Symptoms in Parkinson Disease[a]

Category	Specific Agents and Typical Starting Dose	Therapeutic Uses				Most Common Adverse Effects Other Than Dyskinesia
		Early Symptomatic	Levodopa Adjunct	Wearing Off	Dyskinesia	
Levodopa preparations	Immediate-release **carbidopa-levodopa** (25/100 mg, 3 times/d)	● green	○	● green	● purple	Nausea
	Controlled-release **carbidopa-levodopa** (25/100 mg, 3 times/d)	● green	○	● green	● purple	Nausea
	Extended-release **carbidopa-levodopa** (23.75/95 mg, 3 times/d for 3 d; then 36.25/145 mg, 3 times/d for 3 d)	● green	○	● green	● green	Nausea
	Enteral suspension **carbidopa-levodopa** (clinical titration)		○	● green	● green	Nausea
	Inhaled **levodopa** (as needed)		○	● yellow [b]		Nausea, upper respiratory tract infection
Nonergot dopamine agonists[c]	Immediate-release **pramipexole** (0.125 mg, 3 times/d, increasing weekly) or extended-release **pramipexole** (0.375 mg, 1 time/d, increasing weekly)	● green	● green	● green	● purple	Orthostatic hypotension, dizziness, nausea, sleepiness
	Immediate-release **ropinirole** (0.25 mg, 3 times/d, increasing weekly) or extended-release **ropinirole** (2 mg, 1 time/d, increasing weekly)	● green	● green	● green	● purple	Orthostatic hypotension, dizziness, nausea, sleepiness
	Transdermal **rotigotine** (2 mg/24 h)	● green	● green	● green	● purple	Site reactions, dizziness, orthostatic hypotension
	Injected **apomorphine** (as needed)			● green		Site reactions, dizziness, orthostatic hypotension
Monoamine oxidase-B inhibitors	**Selegiline** (5 mg, 2 times/d)	● green	● yellow	● yellow	● purple	Nausea, dizziness, insomnia
	Rasagiline (1 mg every morning)	● green	● green	● green	● purple	Orthostatic hypotension, nausea
	Safinamide (50 mg/d)	● yellow	● yellow	● green	● purple	Nausea
	Zonisamide (25 to 200 mg/d)[d]			● green		Sleepiness, loss of appetite
Catechol-O-methyltransferase inhibitors	**Entacapone** (200 mg with each levodopa dose)			● green	● purple	Nausea, diarrhea
	Opicapone (50 mg every night)[e]			● green	● purple	Falls, insomnia, orthostatic hypotension
	Tolcapone (100 mg, 3 times/d)[f]			● green	● purple	Gastrointestinal symptoms, orthostatic hypotension, sleep disorders
Other	**Anticholinergics** (eg, trihexyphenidyl, benztropine; dose varies)[g]	● green	● green			Dizziness, anxiety
	Amantadine (dose varies by formulation)[h]	● green	● green		● green	Orthostatic hypotension, hallucinations, edema, gastrointestinal symptoms
	Istradefylline (20 mg/d)			● green		Nausea, hallucinations
	Clozapine (12.5-25 mg every night)[f]				● green	Sleepiness, dizziness, tachycardia, constipation, orthostatic hypotension, sialorrhea

● green "Clinically useful" or "possibly useful"[i]   ● yellow Used in clinical practice outside of evidence base   ● purple Dose reduction or adjustment may reduce dyskinesia   ○ Not relevant

[a] Inclusion in the table does not imply US Food and Drug Administration (FDA) approval for any specific indication.

[b] Not included in International Parkinson and Movement Disorders Society review; approved by the FDA for motor fluctuations ("off" time).

[c] Conversely, ergot dopamine agonists include cabergoline, pergolide, and bromocriptine are typically not used given adverse event risks including cardiac valvulopathy.

[d] Mechanism of action not completely certain; inhibition of monoamine oxidase-B is thought to be one contributing mechanism. Zonisamide is approved for use in Parkinson disease in Japan, but it is not commonly used for this purpose in the United States, where it is approved for use as an antiepileptic medication.

[e] Under review by the FDA at time of publication.

[f] Requires specialized monitoring (liver function for tolcapone; complete blood count for clozapine).

[g] Anticholinergic agents should be used sparingly in clinical practice given common adverse effects such as cognitive slowing.

[h] Amantadine is more commonly used for treatment of dyskinesias rather than as early symptomatic or adjunctive treatment.

[i] Indicates usefulness as determined by the International Parkinson and Movement Disorder Society Evidence-Based Medicine Review.[43]

Figure 5. Proposed General Approach to Treating Motor Symptoms in Parkinson Disease

Parkinson disease motor symptoms	
Bradykinesia with or without rigidity	Tremor

Initial medical therapy

Tremor and/or bradykinesia options

Levodopa preparations	Dopamine agonists	Monoamine oxidase-B inhibitors

Tremor only

Anticholinergic agents (eg, trihexyphenidyl)

Subsequent medical therapy

Increasing doses and add-on therapies for "wearing off"

Levodopa preparations	Monoamine oxidase-B inhibitors	Istradefylline
Dopamine agonists	Catechol-O-methyltransferase inhibitors	Amantadine (primarily for dyskinesia)

Advanced therapy

Tremor and/or bradykinesia options

Levodopa carbidopa enteral suspension infusion	Unilateral or bilateral deep brain stimulation • Subthalamic nucleus • Globus pallidus interna

Tremor only

Unilateral focused ultrasound thalamotomy

Unilateral or bilateral deep brain stimulation (thalamus)

Rehabilitative therapy

For all symptoms and across all disease stages

Exercise

Physical therapy

Occupational therapy

Speech therapy

Initial treatment of Parkinson disease motor symptoms can occur with levodopa preparations, dopamine agonists, or monoamine oxidase-B inhibitors, with recent evidence favoring levodopa for many individuals with Parkinson disease. In young, cognitively intact individuals with Parkinson disease, anticholinergic agents may be used for tremor. However, they are commonly associated with adverse events such as confusion and dry mouth, and dry eyes. Exercise and rehabilitative therapies are important across Parkinson disease stages. With progression, individuals with Parkinson disease will require increasing doses of their initial therapy and the addition of other therapies with complementary mechanisms of action. If "wearing off" (worsening symptoms and functional impairment when a medication dose wears off) and dyskinesias cause functional impairment despite optimal medication dosing, advanced therapies such as deep brain stimulation or therapy with levodopa-carbidopa enteral suspension (via percutaneous endoscopic transgastric jejunostomy) can be used. Thalamic procedures (unilateral focused ultrasound thalamotomy or deep brain stimulation) only help tremor, not other parkinsonian features.

treadmill exercise,[55] strength training,[53] aerobic exercise,[53] music- and dance-based approaches,[53,56,57] and tai chi.[58] Diverse exercise approaches may benefit different motor aspects of Parkinson disease. Additionally, physiotherapy, occupational therapy, and speech therapy (for speech and swallowing) are useful.[43,53,59] Therapy interventions can help maintain or improve motor symptoms, balance, gait, and function and provide strategies for addressing hypophonia and dysphagia. Referrals for interdisciplinary therapy consultations are an important component of quality care in Parkinson disease.[60]

Advanced Therapies for Motor Symptoms
Deep brain stimulation, MRI-guided focused ultrasound, and therapy with levodopa-carbidopa enteral suspension require specialty center assessments to determine patient eligibility, perform the procedures, and manage ongoing medication and device optimization (eg, programming stimulation parameters in deep brain stimulation or titrating dosing of the enteral suspension). These approaches are useful for individuals with Parkinson disease who have medication-responsive motor symptoms but who have complications such as off periods or dyskinesias that are not

responsive to medication adjustments. Deep brain stimulation and focused ultrasound targeting the thalamus can reduce medication-refractory tremor.

Deep brain stimulation involves surgical placement of unilateral or bilateral leads (wires) transcranially in the subthalamic nucleus or the globus pallidus interna. These leads are attached to a battery in the chest, similar to a pacemaker battery. Following surgical recovery, individuals with deep brain stimulation attend programming visits to optimize stimulation parameters and medications. Deep brain stimulation is used to treat the effects of wearing off that involve motor symptoms, tremor, and dyskinesia.[43] Meta-analyses suggest that deep brain stimulation improves on-medication motor scores on the Unified Parkinson Disease Rating Scale (range, 0-108 points; minimal clinically important difference, 2.3-2.7 points[61]) by 4.56 points (95% CI, 3.11-6.00) vs best medical therapy and off-medication scores by 15.50 points (95% CI, 12.60-18.39).[62]

In tremor-predominant Parkinson disease, some clinicians use ventralis intermedius nucleus (thalamic) deep brain stimulation, MRI-guided focused ultrasound,[63] or less commonly, traditional thalamotomy. The thalamic target is only for tremor,

not other Parkinson disease symptoms. Focused ultrasound uses highly focused ultrasound beams to burn the target (the thalamus) while using MRI to target and monitor the extent of the lesion. The resulting lesion improves on-medication tremor scores by 62% (interquartile range, 22%-79%)[63] but can only be performed unilaterally due to risks of adverse events such as worsening speech and balance.

Characteristics associated with worse deep brain stimulation outcomes include older age (≥75 years), cognitive impairment (particularly dementia), and the presence of levodopa-unresponsive symptoms (eg, gait, balance disturbance).[64] Questionnaire-based and online screening tools can help identify and triage appropriate candidates for deep brain stimulation.[65,66] The most effective screening technique is an experienced multidisciplinary team evaluation and discussion of potential risks and benefits, surgical approach, brain target selection, and optimization of medications and stimulation.

Levodopa-carbidopa enteral suspension also treats motor fluctuations and dyskinesias.[43] Levodopa-carbidopa enteral suspension is a levodopa gel administered continuously via a pump through a percutaneous endoscopic transgastric jejunostomy, resulting in more continuous plasma levodopa levels than oral dosing. Pump programming occurs at trained centers. Treatment with levodopa-carbidopa enteral suspension reduces off times (−1.19 hours per day [95% CI, −2.25 to −0.12]) and increases time when symptoms are well-controlled without troublesome dyskinesias (0.55 hours per day [95% CI, 0.20-0.90]).[67,68] Adverse events relating to the percutaneous endoscopic transgastric jejunostomy are common and include complications of device insertion, abdominal pain, tube dislocation, and knotting.[68]

Pharmacologic Treatment for Nonmotor Symptoms

Most drugs used to treat nonmotor symptoms work via neurotransmitters other than dopamine (Table 1). Symptomatic treatments for nonmotor symptoms are similar to treatments for these symptoms in general (non-Parkinson disease) populations. Evidence for these treatments specifically in people with Parkinson disease is variable.

For Parkinson disease dementia, the International Parkinson and Movement Disorder Society designates rivastigmine as clinically useful,[69] based on a double-blind clinical trial randomizing 362 individuals with Parkinson disease dementia to rivastigmine (3-12 mg daily) and 172 individuals to placebo.[70] Participants receiving rivastigmine had a mean improvement of 2.1 points on the 70-point Alzheimer Disease Assessment Scale vs a 0.7-point decline in the placebo group (P < .001). Donepezil and galantamine are designated as possibly useful because of limited evidence to support their efficacy in Parkinson disease. There is no evidence to support memantine or treatment of mild cognitive impairment.[69]

Selective serotonin reuptake inhibitors, selective serotonin norepinephrine reuptake inhibitors, and tricyclic antidepressants may all be useful for treating depression in Parkinson disease.[69] Pramipexole, a dopamine agonist, is useful for depression in some individuals.[69] Nonpharmacologic approaches such as cognitive-behavioral therapy and repetitive transcranial magnetic stimulation may be useful for treating depression in Parkinson disease.[69] There are no randomized clinical trials for treating anxiety in Parkinson disease.[69] Approaches typically mimic those in general populations. There are no adequate pharmacological treatments for apathy in individuals with Parkinson disease.[69]

Treating psychosis in Parkinson disease should begin with weaning potentially contributing medications, such as anticholinergics, amantadine, dopamine agonists, MAO-B inhibitors, and sometimes levodopa. Occasionally weaning is limited by bothersome reemergence of previously controlled Parkinson disease symptoms. If psychosis persists and requires treatment, there are 3 main options: pimavanserin, clozapine, and quetiapine.[69] Other antipsychotic medications should be avoided given adverse event risks including worsening parkinsonism and death.[69,71,72] Pimavanserin, a selective inverse serotonin 5-HT2A receptor agonist, is the only FDA-approved medication for Parkinson disease psychosis, but safety data beyond 6 weeks are lacking, and delivery requires a specialty pharmacy.[69,73] Clozapine works via serotonergic and dopaminergic pathways. Multiple randomized clinical trials show that clozapine improves Parkinson disease psychosis.[69] However, prescribers and patients must register in the Risk Evaluation and Mitigation Strategy program, and regular (initially, weekly) monitoring for neutropenia is required. Multiple studies failed to show benefits of quetiapine on Parkinson disease psychosis, but many had small sample sizes.[69] Quetiapine is the most convenient of the antipsychotic drugs to prescribe, so it is commonly used in clinical practice despite the absence of observed benefit in clinical trials. All antipsychotic drugs, including those safest in Parkinson disease, have black box warnings regarding use in individuals with dementia.

Insomnia, fatigue, and daytime sleepiness are common and may be disabling in Parkinson disease, but no pharmacological treatments for these symptoms have established efficacy.[69,74] Approaches to insomnia are those used for general geriatric populations. Rapid eye movement sleep behavior disorder is treated with melatonin (6-15 mg) as a first-line agent and clonazepam (0.5-1.0 mg) if needed, but high-quality evidence is lacking.[16]

Treatments for autonomic features are similar to therapies in other conditions. Fludrocortisone, midodrine, and droxidopa are all possibly useful for orthostatic hypotension.[69] Probiotics and prebiotic fiber, macrogol, and lubiprostone have limited evidence for treating constipation in Parkinson disease.[69] Various prokinetics and laxatives are commonly used.[75] There are few Parkinson disease–specific studies for treating urinary symptoms. Sildenafil is useful for treating sexual dysfunction.[69] Botulinum toxin injections have the most evidence for treating sialorrhea in Parkinson disease,[69] but glycopyrrolate and sublingual atropine are also prescribed.[69,76]

Selection of optimal medical treatments for nonmotor symptoms is based on the likelihood of efficacy and adverse effect profiles. Agents with anticholinergic properties may improve urinary dysfunction or sialorrhea but contribute to confusion and hallucinations, particularly in individuals with cognitive impairment. Similarly, benzodiazepines may help sleep or anxiety but could worsen cognitive function. There is little data on the use of cannabinoids, but several clinical trials are ongoing.

Palliative Care

Palliative care in Parkinson disease includes treatment of bothersome motor and nonmotor symptoms, advance care planning,

caregiver assessments, and hospice referrals.[77] Hospice referral timing is based on clinical assessments of functional decline (eg, needing assistance with all ADLs), loss of ambulation, incontinence, recurring infections, and insufficient oral intake.

Disease-Modifying Therapy
Currently, no pharmacologic therapies prevent or delay Parkinson disease progression.[43] A recent phase 2 randomized clinical trial of high-intensity treadmill exercise in individuals with new-onset Parkinson disease found significantly less worsening of motor function in the high-intensity exercise group than in the usual care group.[78] Further study is needed to investigate whether exercise modifies Parkinson disease progression.

Limitations
First, this review was developed from published systematic reviews and meta-analyses. The literature search used validated PubMed filters, but use of these filters may have missed some relevant publications. Second, not all aspects of Parkinson disease di-

agnosis and treatment were discussed (eg, approaches to diagnosing aspects of Parkinson disease such as depression, cognitive impairment). Third, there is substantial heterogeneity in individual approaches to treating Parkinson disease. Fourth, high-quality Parkinson disease–specific evidence for treating most nonmotor symptoms is lacking.

Conclusions

Parkinson disease is a heterogeneous disease with rapidly and slowly progressive forms. Treatment involves pharmacologic approaches (typically with levodopa preparations prescribed with or without other medications) and nonpharmacologic approaches (such as exercise and physical, occupational, and speech therapies). Approaches such as deep brain stimulation and treatment with levodopa-carbidopa enteral suspension can help individuals with medication-resistant tremor, worsening symptoms when the medication wears off, and dyskinesias.

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