Chapter 78: Parkinson Disease

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CHAPTER SUMMARY FROM THE PHARMACOTHERAPY HANDBOOK

For the Chapter in the Schwinghammer Handbook, please go to Chapter 58, Parkinson Disease.

KEY CONCEPTS

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1. To optimize long-term therapeutic outcomes, minimize adverse effects, and improve quality of life for individuals with idiopathic Parkinson disease (PD), clinicians need to (1) continually access motor and nonmotor symptoms, (2) thoughtfully consider initial and adjunctive therapies, and (3) continually adjust medication dosages throughout the course of this illness.
2. In general, treatment should be initiated when the disease begins to interfere with activities of daily living, employment, or quality of life.
3. Surgery is an option for patients who require additional symptomatic relief or control of motor complications.
4. Anticholinergic medication can be useful for mild symptoms of PD but, due to adverse medication effects, it should be used with caution in older patients and those with pre-existing cognitive difficulties.
5. Monotherapy with amantadine or the irreversible monoamine oxidase type B (MAO-B) inhibitors provide symptomatic benefit, but less than that of dopamine agonists or carbidopa/levodopa (L-dopa).
6. Carbidopa/L-dopa is the most effective medication for symptomatic treatment.
7. Most patients treated with carbidopa/L-dopa will develop motor complications (eg, fluctuations and dyskinesias).
8. MAO-B inhibitors (irreversible and reversible), catechol-*O*-methyltransferase (COMT) inhibitors, and adenosine A2 receptor antagonists are useful add-on therapies to attenuate motor fluctuations in patients treated with carbidopa/L-dopa.
9. Amantadine is a useful add-on agent to attenuate dyskinesias.
10. Dopamine agonists are effective and, compared to L-dopa, associated with less risk of developing motor complications. They do, however, carry a greater risk for psychiatric symptoms, such as hallucinations and impulse control disorders.

BEYOND THE BOOK

BEYOND THE BOOK

Refer to Chapter 69: Parkinson Disease: Slow and Shaky Level III in *Pharmacotherapy Casebook: A Patient-Focused Approach* and read the initial patient presentation to answer the following questions.

(1) What medications may be considered for treatment of this patient's uncontrolled PD? List the different medication options along with specific treatment considerations for this particular patient such as adverse effects, tolerability concerns, etc.

(2) This patient shares that they just saw a commercial for a new medication for Parkinson disease, opicapone, and wants to know if this would be an option right now. Explain why opicapone would not be an initial medication choice for this patient.

(3) Upon closer evaluation of the patient case, you notice that there is no history of past medications this patient has used. You would like to get this information to assess for medication-induced parkinsonism. Create a list of medications that can cause parkinsonian symptoms, and the mechanism by which they can induce symptoms.

INTRODUCTION

The presence of bradykinesia (slowness of movements) along with tremor at rest, rigidity, and postural instability (instability of balance) is considered the hallmark motor features of idiopathic Parkinson disease (PD), a disorder of the extrapyramidal system. These clinical features of PD were adeptly described in 1817 by James Parkinson.[1]

EPIDEMIOLOGY

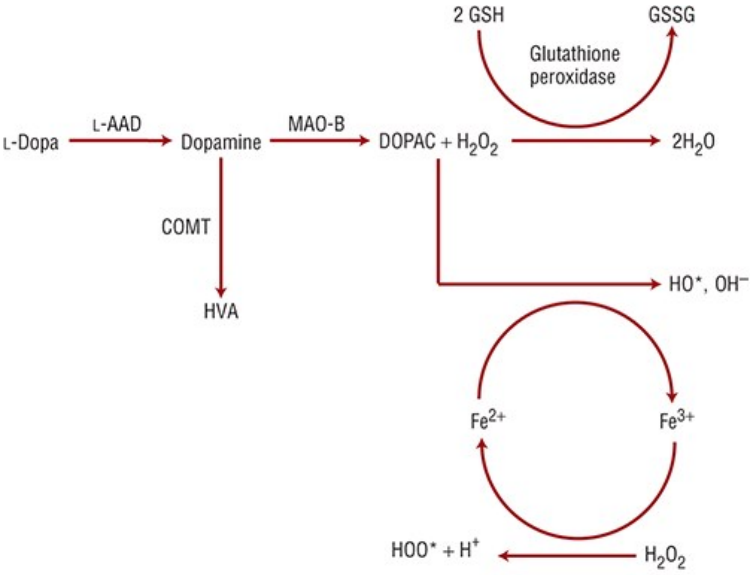
Up to 1 million individuals in the United States have PD, and this is only projected to increase over time.[2] The overall incidence rate of PD (ie, number of persons newly diagnosed with PD per year) is age- and sex-dependent. For individuals between the ages of 40 and 49 years, there are approximately 3 per 100,000 persons diagnosed with PD. However, for females in the ninth decade of life (ie, 80-89 years), the prevalence is 10 per 100,000 persons compared to males with an incidence of 250 per 100,000 persons.[3] The usual age at the time of diagnosis ranges between 55 and 65 years, and overall, PD affects less than 0.5% of people in their 60s and 2.5% of those older than 80 years.[4]

ETIOLOGY

Parkinson disease occurs sporadically, and the true etiology is unknown. However, the etiopathogenesis of PD likely involves environmental and genetic factors.[5] At the cellular level, degeneration of dopaminergic neurons (axons and soma) projecting from the substantia nigra pars compacta (SNc) to the striatum (caudate nucleus and putamen) is a hallmark of PD.[6] Additionally, neurons in autonomic ganglia, enteric nervous system, limbic system, olfactory bulb, spinal cord, and neocortex are affected. The underlying mechanisms are interconnected and multifaceted with the involvement of toxic biochemical reactions (excitotoxicity, nitric oxide toxicity, oxidative stress), abnormal cellular and cell death signaling pathways (apoptosis, inflammation), dysfunctional organelles (lysosomes, mitochondria), and dysfunctional protein degradation systems (autophagy, ubiquitin proteasomal system) resulting in cytoplasmic protein (α-synuclein) accumulation.[7] Several of these mechanisms result in excessive production of free radicals which exert stress on cells by damaging membranes and organelles. The SNc and the striatum are regions characterized by high levels of oxidative stress due to dopamine degradation and the Fenton reaction (Fig. 78-1).[8] Normally, intrinsic antioxidants (eg, glutathione) buffer against oxidative stress, but in PD, this buffer might be impaired or overwhelmed. Pathologic findings reveal a correlation between the extent of nigrostriatal dopamine loss and the severity of certain PD motor features (eg, bradykinesia and rigidity). At the time of PD onset, the estimated loss of SNc neurons and striatal dopamine content are 30% and 50%, respectively.[9] The loss of striatal dopamine exceeds the loss of SNc cell bodies because cellular degeneration begins in the distal presynaptic axon terminals and proceeds over time toward the cell body/soma (ie, "dying back" axonopathy).[9]

FIGURE 78-1

Dopamine metabolism results in hydrogen peroxide (H_2O_2) formation. In the Fenton reaction, H_2O_2 accepts an electron from ferrous iron (Fe^{2+}) to produce ferric iron (Fe^{3+}) and the hydroxyl radical (HO^*). Fe^{3+} is reduced back to Fe^{2+} by another molecule of H_2O_2, forming a hydroperoxyl radical (HOO^*). The radicals damage cell membranes and organelles (eg, mitochondria) and also induce apoptotic signaling. (COMT, catechol-*O*-methyltransferase; DOPAC, 3,4-dihydroxyphenylacetic acid; GSH, glutathione; GSSG, glutathione disulfide; H^+, proton; H_2O, water; HVA, homovanillic acid; L-AAD, L-aromatic amino acid decarboxylase; OH^-, the hydroxide ion; MAO-B, monoamine oxidase B).



Source: Joseph T. DiPiro, Gary C. Yee, Stuart T. Haines, Thomas D. Nolin, Vicki L. Ellingrod, L. Michael Posey: *DiPiro's Pharmacotherapy: A Pathophysiologic Approach, 12e*

Aging, genetic constitution, lifestyle, and environmental factors likely increase an individual's risk for PD.[7,10] Epidemiologic research links environmental factors (eg, chronic exposure to pesticides), with an elevated risk. Cigarette smoking and caffeine consumption are consistently associated with a lower risk.[11,12] Genetic polymorphisms and epigenetics also modify an individual's risk for PD.[5,7,13] It is known that pesticide exposure and genetic forms of PD (eg, leucine-rich repeat kinase 2 [LRRK2], parkin, and PTEN-induced putative kinase 1 [PINK1]) are associated with mitochondrial dysfunction and oxidative stress.[7]

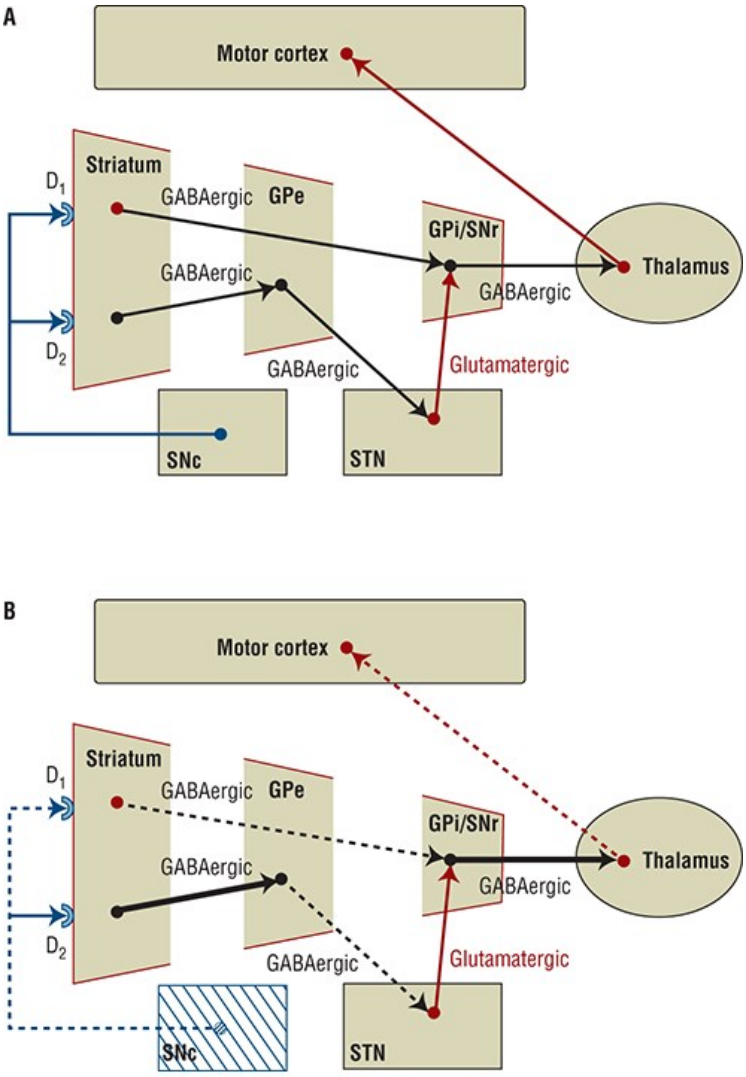
PATHOPHYSIOLOGY

A function of the basal ganglia (composed of subcortical structures including the substantia nigra, striatum, globus pallidus, and subthalamic nucleus [STN]) is to regulate voluntary movement. These subcortical structures exist in duplicate, with one structure on each side of the midline. The substantia nigra consists of two parts: the SNc and pars reticulata (SNr). Neuronal projections from the SNc to the striatum are referred to as the *nigrostriatal pathway*. The striatum conveys signals to the SNr, via the dopamine$_1$ (D_1) direct and the dopamine$_2$ (D_2) indirect pathways (Fig. 76-2A). The SNr (which is closely linked to the globus pallidus interna [GPi]) receives signals from the striatum and conveys final processed signals to the thalamus, which serves as the "gateway" to the motor cortex. When examining the basal ganglia circuitry, it is important to note that striatal D_1 receptors are coupled to adenylate cyclase and mediate postsynaptic depolarization; thus, D_1 receptor activation results in stimulation of the striatal GABAergic neurons.[14,15] Increased activity of the direct pathway results in increased movement. In contrast, striatal D_2 receptors are coupled to a guanosine triphosphate-binding protein and mediate postsynaptic hyperpolarization; thus, D_2 receptor activation results in inhibition of striatal GABAergic neurons, and a net reduction in movement.[14] Additionally, adenosine A2A receptors (A2AR) are located in the striatopallidal GABAergic neurons within this indirect pathway.[15] In PD, reduced dopaminergic activation of D_1 and D_2 receptors and the sequential downstream effect on signaling pathways result in a net inhibitory tone on the thalamus (Fig. 76-2B). Dopaminergic therapies help restore functional activity within the D_1 and D_2 pathways with the latter primarily responsible for mediating clinical improvements. Antagonism of A2ARs (ie, inhibition of the indirect pathway) can result in

prolongation of dopaminergic action in PD and is the mechanism of action behind the non-dopaminergic treatment option, istradefylline.[15,16]

FIGURE 78-2

(*A*) Dopaminergic pathways of the basal ganglia–thalamocortical circuit. Activation of D_1 and D_2 receptors results in depolarization and hyperpolarization, respectively, of postsynaptic neurons. (Red dots and lines represent excitatory input; black dots and lines represent inhibitory input.) (*B*) In Parkinson's disease, degeneration of presynaptic nigrostriatal neurons results in inhibition of the thalamocortical circuit and reduced signaling to the motor cortex. (*Dashed lines* represent reduction of neurotransmitter activity; GPe, globus pallidus externa; GPi, globus pallidus interna; SNc, substantia nigra pars compacta; SNr, substantia nigra pars reticulata; STN, subthalamic nucleus.)



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Within the SNc, histopathologic features of PD are (1) depigmentation of dopamine-producing neurons (ie, loss of SNc neurons) and (2) presence of Lewy bodies (cytoplasmic filamentous aggregates composed of the protein α-synuclein) in the remaining neurons.[6] Lewy bodies appear in association with adjacent gliosis (ie, a response of glial cells to injury), and the formation and spread of Lewy pathology is proposed to occur in stages. In the premotor stage of PD, Lewy bodies are found in the medulla oblongata, locus coeruleus, raphe nuclei, enteric nervous system, and olfactory bulb. This provides anatomic correlates to observations that mood (eg, anxiety, depression) and peripheral symptoms (eg, constipation, impaired olfaction) are present in premotor stages of PD. Lewy pathology develops peripherally in the enteric nervous system and olfactory system and may spread anterogradely or retrogradely to the brain.[17] With the development of Lewy pathology in the midbrain (particularly the SNc), motor features begin to

emerge. In advanced stages, Lewy pathology spreads to the cortex, and this may correlate with cognitive and additional behavior changes. Recent investigations have shown that α-synuclein pathology can propagate into adjacent healthy neurons in a nontoxic infectious manner that results in subsequent neuronal toxicity.[3,18]

The synaptic organization of the basal ganglia also involves a variety of other neurotransmitters and neuromodulators, including acetylcholine, adenosine, enkephalins, γ-aminobutyric acid (GABA), glutamate, serotonin, and substance P. The potential role for medication modulation of these other neurotransmitters and receptor types is an active area of research and novel therapeutic discovery.[19]

Atypical parkinsonian disorders such as multiple system atrophy and progressive supranuclear palsy are characterized by damage to postsynaptic striatal neurons and dopamine receptors. Therefore, dopaminergic therapies are less efficacious in atypical parkinsonism.

CLINICAL PRESENTATION

CLINICAL PRESENTATION: Idiopathic PD

General Features

- The patient exhibits bradykinesia (slowness of movements) and at least one of the following: resting tremor, rigidity, or postural instability. Asymmetry of motor features is supportive.

Motor Symptoms

- The patient experiences hypokinetic movements, decreased manual dexterity, difficulty arising from a seated position, diminished arm swing during ambulation, dysarthria (slurred speech), dysphagia (difficulty with swallowing), festinating gait (tendency to pass from a walking to a running pace), flexed posture, “freezing” at initiation of movement, hypomimia (reduced facial animation), hypophonia (reduced voice volume), and micrographia (Fig. 78-3).

Autonomic and Sensory Symptoms

- The patient experiences bladder dysfunction, constipation, diaphoresis, fatigue, olfactory impairment, orthostatic intolerance, pain, paresthesia, paroxysmal vascular flushing, seborrhea, sexual dysfunction, and sialorrhea (drooling).

Mental Status Changes

- The patient experiences anxiety, apathy, bradyphrenia (slowness of thought processes), cognitive impairment, depression, and hallucinosis/psychosis.

Sleep Disturbances

- The patient experiences excessive daytime sleepiness, insomnia, obstructive sleep apnea, and rapid eye movement (REM) sleep behavior disorder.

Laboratory Tests

- No laboratory tests are available to diagnose PD.

Other Diagnostic Tests

- Genetic testing is not routinely helpful.
- Neuroimaging may be useful for excluding other diagnoses.
- Medication history should be obtained to rule out medication-induced parkinsonism.

The clinical diagnosis of PD is based on the presence of bradykinesia and at least one of three other features: muscular rigidity, resting tremor, and/or postural instability (Table 78-1).[20] Asymmetry of motor features is a supportive finding. It is important to note that tremor is not always present at the time of diagnosis, and postural instability typically occurs in later stages of PD. Overall, a diagnosis of PD can be made with a high level of confidence in a patient who has bradykinesia (along with rest tremor and/or rigidity), prominent asymmetry, and a good response to dopaminergic therapy. For the diagnosis of PD, other conditions must be reasonably excluded (see Table 78-1). Medication-induced parkinsonism can mimic PD and is the second most common form of parkinsonism.[21] It is important to assess for recent use of medications, especially medications that block D_2 receptors, such as antipsychotics (eg, haloperidol), metoclopramide, or phenothiazine antiemetics (eg, prochlorperazine).[21] Neurologic conditions that can be mistaken for PD include atypical parkinsonisms and tremor disorders (eg, dystonic tremor, essential tremor). Because the management and prognosis of PD differ from these other conditions, obtaining an accurate diagnosis is important. When the diagnosis is in doubt, referral to a movement disorders specialist is recommended. Currently, efforts are underway to develop and validate diagnostic tools based on personalized clinical, laboratory, imaging, and genomics data.

Parkinson disease develops insidiously and progressively worsens over many years. Tremor of an upper extremity occurring at rest (and occasionally an action or postural tremor) is often the sole presenting complaint. However, only two-thirds of patients with PD have tremor on diagnosis, and some never develop this sign. Tremor in PD is present most commonly in the hands, sometimes with a characteristic pill-rolling motion. Less commonly, tremor may involve the jaw or legs. Like other motor features of PD, resting tremor often begins unilaterally and becomes bilateral with disease progression. Stressful or emotional (either negative or positive) situations often increase the tremor amplitude and severity. Usually, tremor is absent during sleep. Although resting tremor is visibly noticeable in PD and may cause social embarrassment for the patient, it often is the least physically disabling of the motor features.

Rigidity is the increased muscular resistance to passive range of motion and most commonly affects the upper and lower extremities and occasionally the neck. If tremor is present in the affected extremity, the rigidity is associated with a cogwheel or ratchet-like quality upon examination. Facial muscles also are affected, resulting in hypomimia that may be erroneously interpreted as apathy, depression, or unfriendliness.

Hypokinesia is a decreased movement and often described as either bradykinesia (slowness of movement) or akinesia (absence of movement). Movement in PD is often slow throughout an intended action and difficulty with the initiation of movement also occurs. A progressive slowing and decline in dexterity may impair tasks such as hand clapping, finger tapping, and handwriting (Fig. 78-3). Intermittent immobility or akinesia (freezing) is another common characteristic. Freezing is especially likely to occur in situations such as when walking through a narrow doorway or initiating a turn.

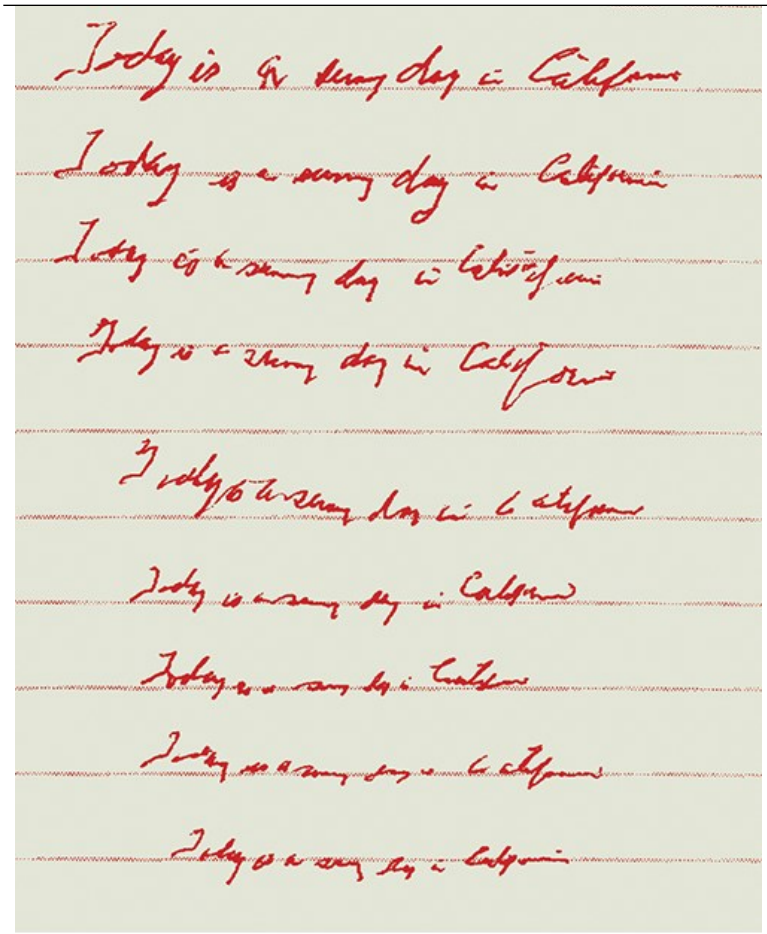
The clinical diagnosis of PD relies on motor findings; however, neuroimaging along with nonmotor markers (eg, REM sleep behavior disorder, olfactory impairment) may someday aid in the detection of PD in premotor or prodromal stages (ie, before onset of motor impairment).[22]

Postural instability, most common in advanced stages of PD, is one of the most disabling problems of PD because it increases the fall risk and is least amenable to pharmacotherapy.[23] Testing for impaired postural responses by means of the pull test (in which a patient is unable to recover balance after sudden backward displacement at the shoulders) can help identify the risk for falling. Many patients with impaired postural responses also have tendencies for propulsive gait with difficulty halting their steps while in motion (festination) and freezing, which also increases the risk of falling.

Nonmotor symptoms are common in PD and must be identified, assessed, managed, and monitored (Table 78-2). These include anxiety, cognitive impairment, constipation, daytime sleepiness, depression, drooling, dysphagia, falling, fatigue, impulsivity, insomnia, orthostatic hypotension, overactive bladder, pain, hallucinations/psychosis, REM sleep behavior disorder, and restless legs syndrome.[24] As a component of managing these nonmotor symptoms, it is important to maintain continuous surveillance of prescription and nonprescription medications for potential adverse effects that can exacerbate, mimic, or precipitate nonmotor symptoms. If feasible, any identified offending medication should be deprescribed.

FIGURE 78-3

Example of micrographia in a patient with Parkinson disease. As the sentence “Today is a sunny day in California” is repeatedly handwritten, progressive diminution of letter size occurs (micrographia). The height of each lined row is approximately 5/16 in. (8 mm).



Source: Joseph T. DiPiro, Gary C. Yee, Stuart T. Haines, Thomas D. Nolin, Vicki L. Ellingrod, L. Michael Posey: *DiPiro's Pharmacotherapy: A Pathophysiologic Approach, 12e*

TABLE 78-1

Diagnostic Criteria and Differential Diagnosis for Parkinson Disease

Parkinson Disease

- Step 1: Presence of bradykinesia and at least one of the following: resting tremor, rigidity, or postural instability
- Step 2: Exclude other types of parkinsonism or tremor disorders (see "Differential Diagnosis" below)
- Step 3: Presence of at least three supportive positive criteria:
  - Asymmetry of motor signs/symptoms
  - Unilateral onset
  - Progressive disorder
  - Resting tremor
  - Excellent response to carbidopa/L-dopa
  - L-dopa response for 5 years or longer
  - Presence of L-dopa dyskinesias

Differential Diagnosis

- Essential tremor
- Pharmacotoxicity (medication-induced)
  - Antiemetics (eg, metoclopramide, prochlorperazine)
  - Antipsychotics (eg, chlorpromazine, fluphenazine, haloperidol, olanzapine, risperidone, thioridazine)
  - Other medications (α-methyldopa, cinnarizine, flunarizine, tetrabenazine)
- Environmental toxicity (eg, manganese, organophosphates)
- Infections (eg, human immunodeficiency virus, subacute sclerosing panencephalitis)
- Metabolic disorder (eg, hypothyroidism, parathyroid abnormalities)
- Neoplasms, strokes, traumatic lesions involving the nigrostriatal pathways
- Normal-pressure hydrocephalus
- Parkinsonism with other neuronal system degenerations
  - Corticobasal ganglionic degeneration
- Multiple-system atrophies
- Progressive supranuclear palsy
- Familial (hereditary) parkinsonism
  - Autosomal dominant
  - α-Synuclein gene mutation (*PARK1* and *PARK4*)
  - L-responsive dystonia
  - Leucine-rich repeat kinase 2 (LRRK2) mutation
  - Rapid-onset dystonia parkinsonism (DYT12)
  - Spinocerebellar ataxias (SCA2, SCA3)
- Autosomal recessive
  - Wilson disease
  - Young-onset parkinsonism (DJ-1, parkin, PINK1)
- X-linked recessive
  - Fragile X tremor/ataxia syndrome (FXTAS)
  - Lubag (DYT3 or Filipino dystonia parkinsonism)

TABLE 78-2

Nonmotor Symptoms and Possible Treatments

Symptoms	Possible Treatments
Anxiety	Cognitive behavioral therapy, selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, minimize "off" times
Cognitive impairment	Eliminate anticholinergic agents, add cholinesterase inhibitor
Constipation	Fiber, hydration, exercise, laxatives, stool softeners
Daytime sleepiness	Proper nighttime sleep hygiene, reduce dose of dopaminergic medications, eliminate anticholinergic agents if possible, referral to sleep specialist to rule outsleep apnea and sleep disorders
Depression	Selective serotonin reuptake inhibitor, serotonin norepinephrine reuptake inhibitor, cognitive behavioral therapy
Drooling	Local injection of botulinum toxin, atropine sublingual drop, glycopyrrolate, ipratropium sublingual spray
Dysphagia	Referral to speech therapist, dysphagia diet, avoid anticholinergic medications, manage dry mouth
Fatigue	Caffeine, armodafinil, modafinil, proper nighttime sleep hygiene, referral to sleep specialist to rule out sleep disorder
Falling	Assess for orthostatic hypotension, referral to physical therapy, assistance with ambulation, minimize risk for bone fractures, treat osteoporosis
Hallucinations/psychosis	Dose reduction and/or elimination of adjunctive medications, especially anticholinergic agents; consider addition of pimavanserin, quetiapine or clozapine; Note: pimavanserin is FDA-approved for psychosis in PD
Impulse control disorder	Discontinue dopamine agonist or add clozapine, quetiapine, or naltrexone
Insomnia	Cognitive behavioral therapy-insomnia; nonbenzodiazepine $GABA_A$ agonists, trazodone
Orthostatic hypotension	Reduce dose of alpha-blockers, dopamine agonist, diuretics, and/or vasodilators, abdominal compression, add salt and water to diet, water boluses, fludrocortisone, midodrine, droxidopa, pyridostigmine
Overactive bladder	Behavioral therapies (eg, bladder training, fluid management, pelvic floor muscle exercises), antimuscarinic agents, mirabegron, intradetrusor injections of botulinum toxin
Pain	Treatment as per type of pain (eg, dystonic, musculoskeletal, neuropathic), minimize "off" times, appropriate referral to orthopedics, physical therapy, pain specialist, rheumatology
REM sleep behavior disorder	Clonazepam, melatonin
Restless legs syndrome	Dopamine agonist at bedtime; gabapentin

FDA, Food and Drug Administration; GABA, γ-aminobutyric acid; PD, Parkinson disease; REM, rapid eye movement.

TREATMENT

Desired Outcomes

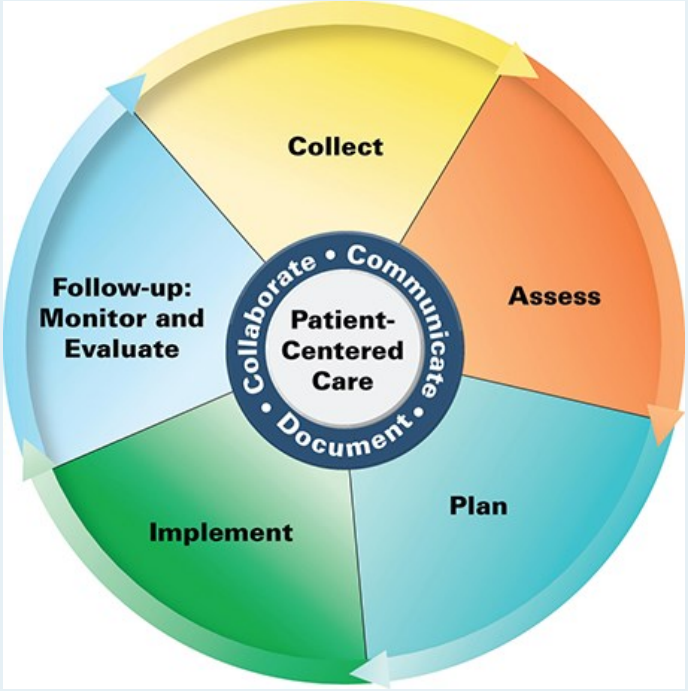
To date, no treatments effectively change the course of PD by slowing or halting its progression (disease modification).[25] Therefore, the goal for management is to improve motor and nonmotor symptoms so that patients are able to maintain the best possible quality of life.[26] Specific objectives to consider when selecting an intervention include preserving the ability to perform activities of daily living, employment, improvement of mobility, minimization of adverse effects, treatment complications, putative disease modification, and improvement of nonmotor features. To accomplish some of these objectives, consultation with a team of specialists is helpful (eg, movement disorders, pharmacotherapy, physical therapy, psychiatry, and sleep medicine).

General Approach to Treatment

1 2 To optimize long-term therapeutic outcomes, minimize adverse effects, and improve quality of life for individuals with PD, clinicians need to (1) continually access motor and nonmotor symptoms, (2) thoughtfully consider initial and adjunctive therapies, and (3) continually adjust medication dosages throughout the course of this illness. Figure 78-4 illustrates a general treatment approach for early and advanced PD. Table 78-3 summarizes antiparkinsonian medications and dosing, and Table 78-4 summarizes monitoring parameters for potential adverse reactions, and Table 78-5 indicates place in therapy for antiparkinsonian medications (ie, monotherapy, adjunctive). Treatment guidelines and monographs are updated frequently to keep up with new information and changes in treatment paradigms.[24,27-30] Additionally, general guidelines and recommendations for geriatric health maintenance and disease prevention (eg, bone health, routine vaccinations, vitamin and mineral supplementations) should also be observed.

PATIENT CARE PROCESS

Patient Care Process for Parkinson Disease



Collect

- Patient characteristics (eg, age, race, sex, hand dominance)

- Patient history (past medical, family, social—dietary habits, alcohol and tobacco use)
- Motor and nonmotor symptoms (see Tables 78-1 and 78-2)
- Current medications, prior medication use for PD and response to prior medications (eg, effectiveness, adverse effects), prior use of dopamine receptor blockers
- Objective data
  - Height, weight
  - Blood pressure and orthostatic blood pressure
  - Labs (eg, serum creatinine [Scr], liver function tests [LFTs])
  - Other diagnostic tests when indicated (eg, neuroimaging)

Assess

- Past and current use of medications associated with medication-induced parkinsonism (eg, antipsychotics, metoclopramide, tetrabenazine)
- Difficulties with performing activities of daily living
- Gait difficulties and fall risk
- Motor or nonmotor symptoms that are most troublesome for the patient
- Appropriateness, effectiveness, and adverse effects of current medications for the motor and nonmotor symptoms of PD
- Presence of motor complications (eg, motor fluctuations, dyskinesias, freezing)

Plan*

- Tailored lifestyle modifications (eg, exercise)
- Pharmacotherapy regimen including specific medications for PD, dose, route, frequency, and duration; specify the continuation and discontinuation of existing therapies (see Table 78-3)
- Monitoring parameters including efficacy (eg, symptom improvement) and tolerability medication-specific adverse effects (see Table 78-4), and time frame
- Patient education (eg, purpose of treatment, lifestyle modification, pharmacotherapy, adverse effects)
- Self-monitoring of symptoms—where and how to record results
- Referrals to other providers when appropriate (eg, physician, physical therapy, speech therapy)

Implement*

- Provide patient education regarding all elements of treatment plan
- Use motivational interviewing and coaching strategies to maximize adherence
- Schedule follow-up

Follow-up: Monitor and Evaluate

- Symptom relief goal attainment

- Presence of adverse effects
- Occurrence of motor complications, falls, and development/progression of nonmotor symptoms
- Patient adherence to treatment plan using multiple sources of information

Collaborate with patient, caregivers, and other healthcare professionals.

FIGURE 78-4

General approach to the management of early to advanced Parkinson disease. (*Age is not the sole determinant for medication choice. Other factors such as cognitive function and overall medication tolerability, especially in older patients should be considered.)

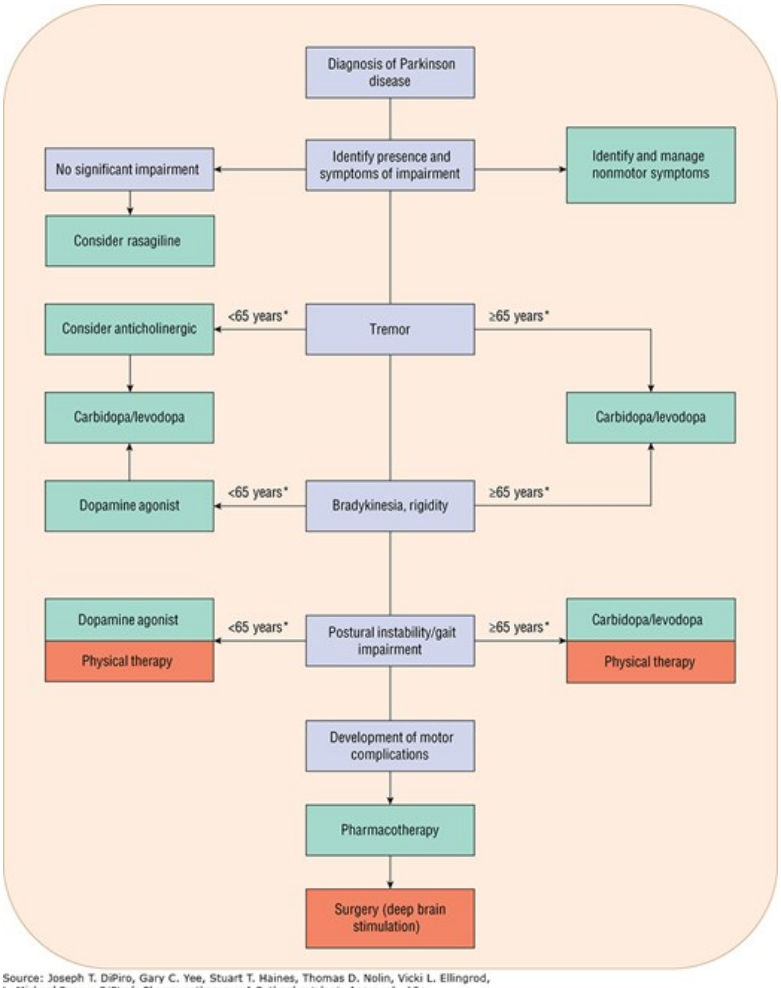


TABLE 78-3

Dosing of Medications Used in Parkinson Disease[a]

Generic Name	Trade Name	Starting Dose[b] (mg/day)	Maintenance Dose[b] (mg/day)	Dosage Forms (mg)
Adenosine-Receptor Antagonist				

Istradefylline	Nourianz	20	20-40	20, 40
Anticholinergic Medications				
Benztropine	Cogentin	0.5-1	1-6	0.5, 1, 2
Trihexyphenidyl	Artane	1-2	6-15	2, 5, 2/5 mL
Carbidopa/Levodopa Products				
Carbidopa/L-dopa	Sinemet	300[c]	300-2,000[c]	10/100, 25/100, 25/250
Carbidopa/L-dopa ODT	Parcopa	300[c]	300-2,000[c]	10/100, 25/100, 25/250
Carbidopa/L-dopa CR	Sinemet CR	400[c]	400-2,000[c]	25/100, 50/200
Carbidopa/L-dopa IR/ER	Rytary	435[c]	435-2,450[c]	23.75/95, 36.25/145, 48.75/195, 61.25/245[d]
Carbidopa/L-dopa enteral suspension	Duopa	1,000[c]	1,000-2,000[c]	4.63/20 per mL
Carbidopa/L-dopa/entacapone	Stalevo	600[e]	600-1,600[e]	12.5/50/200, 18.75/75/200, 25/100/200, 31.25/125/200, 37.5/150/200, 50/200/200
Carbidopa	Lodosyn	25	25-75	25
Levodopa	Inbrija	84	84-420	42[f]
Dopamine Agonists				
Apomorphine	Apokyn	1-3	3-12	30/3 mL[g]
Apomorphine	Kynmobi	10	10-150	10, 15, 20, 25, 30[h]
Bromocriptine	Parlodel	2.5-5	15-40	2.5, 5
Pramipexole	Mirapex	0.125	1.5-4.5	0.125, 0.25, 0.5, 0.75, 1, 1.5
Pramipexole ER	Mirapex ER	0.375	1.5-4.5	0.375, 0.75, 1.5, 2.25, 3, 3.75, 4.5
Ropinirole	Requip	0.75	9-24	0.25, 0.5, 1, 2, 3, 4, 5
Ropinirole XL	Requip XL	2	8-24	2, 4, 6, 8, 12
Rotigotine	Neupro	2	2-8	1, 2, 3, 4, 6, 8
COMT Inhibitors				
Entacapone	Comtan	200-600	200-1,600	200

Opicapone	Ongentys	25-50	50	25, 50
Tolcapone	Tasmar	300	300-600	100, 200
MAO-B Inhibitors				
Rasagiline	Azilect	0.5-1	0.5-1	0.5, 1
Safinamide	Xadago	50	50-100	50, 100
Selegiline	Eldepryl	5-10	5-10	5
Selegiline ODT	Zelapar	1.25	1.25-2.5	1.25, 2.5
Miscellaneous				
Amantadine	Symmetrel	100	200-300	100, 50/5 mL
Amantadine ER	Gocovri	137	274	68.5, 137
Amantadine ER	Osmolex	129	129-258	129, 193, 258

COMT, catechol-*O*-methyltransferase; CR, controlled-release; IR, immediate-release; ER, extended-release; MAO, monoamine oxidase; ODT, orally disintegrating tablet.

[a]Marketed in the United States for Parkinson disease.

[b]Dosages may vary.

[c]Dosages expressed as L-dopa component.

[d]Dosages of Rytary were developed to avoid confusion with other oral carbidopa/L-dopa products that contain L-dopa in multiples of 50 mg.

[e]Dosages expressed as entacapone component.

[f]Capsule containing levodopa dry powder for inhalation.

[g]Sterile solution of subcutaneous injection with supplied pen injector.

[h]Sublingual film of apomorphine.

Data from Reference [31].

TABLE 78-4

Monitoring of Potential Adverse Reactions to Pharmacotherapy for Parkinson Disease

Generic Name	Adverse Medication Reaction	Monitoring Parameter	Comments
Amantadine	• Confusion • Livedo reticularis	Mental status; renal function Lower	Reduce dosage; adjust dose for renal impairment Reversible upon medication discontinuation

		extremity examination; ankle edema	
	Livedo reticularis	Lower extremity examination; ankle edema	Reversible upon medication discontinuation
Benztropine and Trihexyphenidyl	Anticholinergic effects, confusion, drowsiness	Dry mouth, mental status, constipation, urinary retention, vision	Reduce dosage; avoid in elderly and in those with a history of constipation, memory impairment, urinary retention
Carbidopa/L-dopa	• Drowsiness • Dyskinesias • Nausea	• Mental status • Abnormal involuntary movements • Nausea	• Reduce dose • Reduce dose; add amantadine • Take with food (eg, nonprotein snack)
Istradefylline	Insomnia, dizziness, nausea, constipation	Sleep, nausea, bowel movements	• Take in the morning • Take with food
COMT Inhibitors			
Entacapone	Augmentation of L-dopa adverse effects; also diarrhea	See carbidopa/L-dopa; also bowel movements	Reduce dose of L-dopa; antidiarrheal agents
Opicapone	Augmentation of L-dopa adverse effects, constipation	Mental status, abnormal involuntary movements, bowel movements	Reduce dose of L-dopa
Tolcapone	See entacapone; also liver toxicity	See carbidopa/L-dopa; also ALT/AST	See carbidopa/L-dopa; also at start of therapy and for every dose increase, ALT and AST levels at baseline and every 2-4 weeks for the first 6 months of therapy; afterward monitor based on clinical judgment
Dopamine Agonists			
Apomorphine	• Drowsiness • Nausea • Orthostatic hypotension	• Mental status • Nausea • Blood pressure, dizziness upon standing	• Reduce dose • Premedicate with trimethobenzamide • Reduce dose
Bromocriptine	See pramipexole; also pulmonary fibrosis	Mental status; also chest radiograph	Reduce dose; chest radiograph at baseline and once yearly
Pramipexole and Ropinirole	• Confusion • Drowsiness • Edema • Hallucinations/delusions	• Mental status • Lower extremity swelling • Behavior, mental	• Reduce dose • Reduce dose or discontinue medication • Reduce dose or discontinue medication • Titrate dose upward slowly; take with food

	• Impulsivity • Nausea • Orthostatic hypotension	status • Nausea • Blood pressure, dizziness upon standing	
Rotigotine	See pramipexole; also skin irritation at site of patch application	See pramipexole; also skin examination	See pramipexole; rotate patch application site
MAO-B Inhibitors			
Rasagiline	Nausea	Nausea	Take with food
Safinamide	• Nausea • Elevation in blood pressure Insomnia	• Nausea • Blood pressure Sleep	• Take with food • Monitor blood pressure if have a history of uncontrolled hypertension • Take in the morning
Selegiline	• Agitation/confusion • Insomnia • Hallucinations • Orthostatic hypotension	• Mental status • Sleep • behavior, mental status • Blood pressure, dizziness upon standing	• Reduce dose • Administer dose earlier in day • Reduce dose • Reduce dose

ALT, alanine aminotransferase; AST, aspartate aminotransferase; COMT, catechol-*O*-methyltransferase; MAO, monoamine oxidase.

When deciding on therapy for a patient, the following patient-specific factors should be taken into account: age; comorbidities; severity of functional impairment; nonmotor symptoms; patient preferences, therapeutic goals, and outcomes; employment status; medication tolerability; presence of cognitive impairment or motor complications; need for skilled assistance; and health-related economics.[30] The lowest dose of antiparkinsonian medication that provides satisfactory symptomatic results should be used, and for patients already on carbidopa/levodopa (L-dopa), optimization of the regimen should be attempted before adding adjunctive agents (see Table 78-5 for which agents may be used as monotherapy, on demand therapy, and adjunctive therapy). With the increasing motor disability, emergence of medication adverse effects, and changes in severity of nonmotor symptoms, therapy adjustments (eg, dose reductions, medication addition, or discontinuation) are expected, and desired therapeutic endpoints should be routinely reassessed. There are no pharmacogenomic parameters used to guide PD pharmacotherapy.

For mild functional impairment, initial monotherapy may be initiated with an MAO-B inhibitor, such as rasagiline, with the addition of other therapeutic agents as PD motor symptoms progressively worsen. Dopamine agonist monotherapy provides greater symptomatic benefit for patients with mild-to-moderate impairment. However, dopamine agonists are less well tolerated, especially in older patients and for those who are cognitively impaired, intolerant of dopamine agonists, or experiencing moderate or severe functional impairment, carbidopa/L-dopa is preferred.[28-30] Ultimately, all patients will require the use of carbidopa/L-dopa either as monotherapy or in combination with other agents. With the development of motor fluctuations, patients should administer carbidopa/L-dopa more frequently or addition of a catechol-*O*-methyltransferase (COMT) inhibitor, MAO-B inhibitor, A2AR antagonist, or dopamine agonist to the carbidopa/L-dopa regimen should be considered. For management of carbidopa/L-dopa–induced peak-dose dyskinesias, a reduction in L-dopa dose and/or addition of amantadine should be considered. Surgery is considered only in patients who need more symptomatic control or who are experiencing severe motor complications despite pharmacologically optimized therapy.

Ultimately, the treatment plan must evolve as the disease progresses and must include consideration of short-term symptomatic relief as well as long-term effects. Patient education should be communicated with realistic optimism. For example, although there is no cure for PD, medications that can provide relief of symptoms. Nonpharmacologic interventions such as exercise should be encouraged, and problematic nonmotor features of PD should always be addressed.

TABLE 78-5

Summary of Medications for Parkinson Disease Regarding Type: Monotherapy, Adjunctive, and/or On-Demand Options Summary of Medications for Parkinson Disease Regarding Type: Monotherapy, Adjunctive, and/or On-Demand Options

Medication	Class	Monotherapy	Adjunctive	On-Demand
Amantadine	NMDA receptor antagonist	X (rarely)	X	
Apomorphine	Dopamine agonist			X
Benztropine	Anticholinergic	X	X	
Carbidopa	Decarboxylase inhibitor		X[a]	
Entacapone	COMT inhibitor		X[a]	
Istradefylline	Adenosine-receptor antagonist		X	
Levodopa	Dopamine precursor	X	X	X
Opicapone	COMT inhibitor		X[a]	
Pramipexole	Dopamine agonist	X	X	
Rasagiline	MAO-B inhibitor	X	X	
Ropinirole	Dopamine agonist	X	X	
Rotigotine	Dopamine agonist	X	X	
Safinamide	MAO-B inhibitor	X	X	
Selegeline	MAO-B inhibitor		X	
Tolcapone	COMT inhibitor		X[a]	
Trihexyphenidyl	Anticholinergic	X	X	

Of note, table is based upon FDA-approved indications. Some agents may be used off-label as monotherapy/adjunct.

[a]Must be used in combination with Levodopa.

Nonpharmacologic Therapy

A number of nonpharmacological modalities may help improve motor and non-motor symptoms of PD in combination with appropriate pharmacotherapy. Exercise, physiotherapy, yoga, Tai Chi, and dance have evidence to support improvement in PD symptoms.[32] A specific form of physiotherapy that patients with PD may particularly benefit from is the Lee Silvermann Voice Treatment-BIG Therapy. This therapy focuses on increasing the amplitude of movements by focusing on proprioception using sensory cues.[33]

Surgical Therapy

3 Surgery should be considered an adjunct to pharmacotherapy when patients are experiencing frequent motor fluctuations or disabling dyskinesia or tremor despite an optimized medical regimen. There are several patient-selection criteria for surgery, including a diagnosis of L-dopa–responsive PD and absence of cognitive impairment. Anatomic targets include the thalamus, GPi, and the STN. Bilateral, chronic, high-frequency electrical stimulation, also known as deep-brain stimulation (DBS), is the preferred surgical modality.[34]

In DBS surgery, a battery-powered neurostimulator is implanted subcutaneously below the clavicle and provides constant electrical stimulation, via electrode wires, to the targeted brain structure. Thalamic DBS is effective for suppressing tremor (specifically arm tremor), but it does not significantly improve the other parkinsonian features (bradykinesia, rigidity, motor fluctuations, or dyskinesias). Both STN and GPi DBS are associated with improvements in tremor, rigidity, bradykinesia, motor fluctuations, dyskinesia, and activities of daily living; however, STN DBS allows for greater reduction in medications.[35] As with pharmacotherapy, DBS uncommonly improves gait or postural instability.

DBS procedures require routine adjustment of the electrical stimulation parameters (eg, voltage, frequency, and pulse width) to achieve optimal control while minimizing adverse effects. The electrical stimulation parameters (or "electrical dosage") are adjusted via a programmable handheld device to meet each patient's needs and are performed by physicians as well as other trained individuals, including nurse practitioners and clinical pharmacists.

Pharmacologic Therapy

Anticholinergic Medications

4 Dopamine provides negative feedback to acetylcholine neurons in the striatum; therefore, degeneration of nigrostriatal dopamine neurons affects striatal cholinergic interneuron activity. Recent research investigated the effect of dopamine loss on the striatal interneurons in mice models. Initially, the striatal interneurons decreased acetylcholine production slightly, but with the even greater loss of dopamine (which occurs throughout the progression of PD), the balance among the two neurotransmitters shifted to greater acetylcholine levels.[36] This increased cholinergic activity is believed to contribute to the tremor of PD. The anticholinergic medications (eg, benztropine and trihexyphenidyl) are considered effective against tremor, but no more so than dopaminergic agents.[28] Sometimes dystonic symptoms associated with PD are also improved by anticholinergic agents. Use of anticholinergic agents is limited due to the development of intolerable anticholinergic adverse effects (see Table 78-4), necessitating medication discontinuation. Younger patients are better able to tolerate anticholinergic adverse effects, whereas this medication class is avoided in patients with advanced age, pre-existing cognitive deficits, and dysphagia.[37,38]

Amantadine

5 Although amantadine can be used as monotherapy for the management of tremor, rigidity, and bradykinesia, it is most often used adjunctively for management of L-dopa–induced dyskinesia and in patients experiencing "off" episodes[28,29,39] (Table 78-3). The precise mechanism of action of amantadine for management of PD is unknown, but enhancement of dopamine release from presynaptic terminals and inhibition of glutamatergic *N*-methyl-D-aspartate (NMDA) receptors are implicated.[40] The antidyskinetic properties of amantadine are presumed to be mediated by antiglutamate properties which, in the setting of dyskinesias, dominate over dopaminergic properties. There are currently three different formulations of amantadine available for use; an immediate release (IR) formulation and two different extended release (ER) products. Amantadine immediate-release is typically administered 300 mg/day in divided doses, whereas the extended-release formulations allow for once a day dosing (see Table 78-3).[41] Amantadine is eliminated renally, and a reduced dose should be administered when renal dysfunction is present (eg, amantadine immediate-release 100 mg/day with creatinine clearances of 30-50 mL/min [0.50-0.84 mL/s], 100 mg every other day for creatinine clearances of 15-29 mL/min [0.25-0.49 mL/s], and 200 mg every 7 days for creatinine clearances of less than 15 mL/min [0.25 mL/s], and patients on hemodialysis).[42]

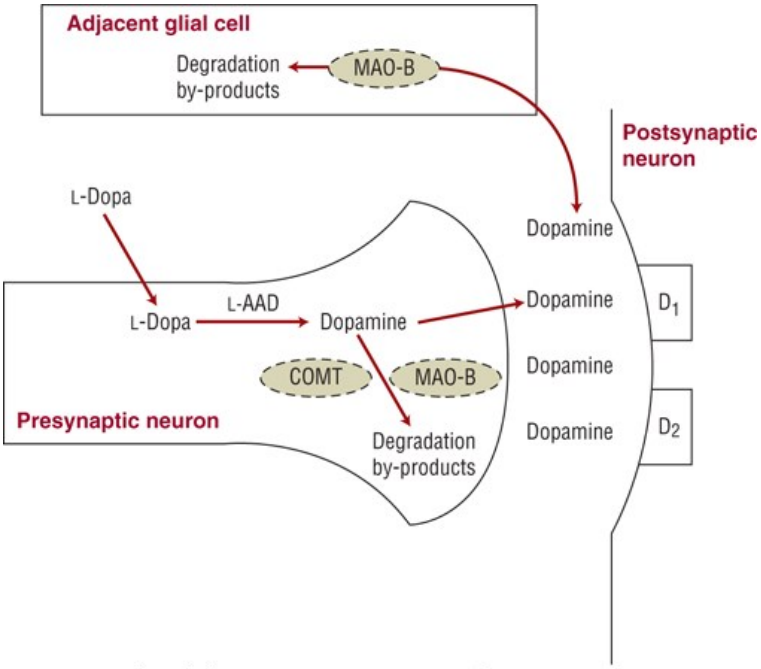
Adverse effects of amantadine include confusion, dizziness, dry mouth, and hallucinations with elderly patients being particularly prone to develop confusion.[43,44] Not uncommonly, amantadine may cause livedo reticularis, a reversible condition characterized by diffuse mottling of the skin affecting the upper or lower extremities and often accompanied by lower-extremity edema (see Table 78-4).[45,46]

Carbidopa/L-Dopa

L-Dopa is the immediate precursor of dopamine and, in combination with a peripherally acting L-amino acid decarboxylase inhibitor (carbidopa or benserazide), remains the most effective medication for the symptomatic treatment of PD.[28,29] In the United States, L-dopa is combined with carbidopa as L-dopa crosses the blood–brain barrier, whereas carbidopa does not, and the carbidopa then reduces the unwanted peripheral conversion of L-dopa to dopamine. As a result, increased amounts of L-dopa are transported into the brain, and the peripheral adverse effects of dopamine, such as nausea, are reduced. In the SNc, L-dopa is converted to dopamine by the enzyme L-amino acid decarboxylase and inactivated by the enzymes MAO and COMT (Figs. 76-1 and 76-5).

FIGURE 78-5

Dopamine synthesis and metabolism within the striatal neurons. See also Fig. 78-1 for additional details. (COMT, catechol-*O*-methyltransferase; D_1-D_2, dopamine receptors; L-AAD, L-aromatic amino acid decarboxylase; L-Dopa, levodopa; MAO-B, monoamine oxidase B.)



Regardless of what the initial therapeutic agent is, ultimately all patients with PD will require L-dopa. Regarding carbidopa, about 75 mg/day is required to sufficiently inhibit the peripheral activity of L-amino acid decarboxylase, but some patients require more.[47] Therefore, the usual initial maintenance carbidopa/L-dopa regimen is 25/100 mg three times daily. As the motor features of PD become progressively more severe, use of higher dosages is required. There is no maximum allowable total daily L-dopa dose; however, in patients with severe PD, the usual maximal dose tolerated is approximately 1,000 to 1,500 mg/day. Slow buildup of dose (eg, increments of 100 mg L-dopa per week) can help minimize treatment-emergent adverse effects, such as drowsiness and nausea (see Table 78-4).

Various formulations of carbidopa/L-dopa are available (see Table 78-3). For patients with difficulty swallowing intact tablets, an orally disintegrating

tablet (ODT) preparation of carbidopa/L-dopa is available, and while this formulation rapidly dissolves on contact with saliva, the carbidopa/L-dopa does not undergo transmucosal absorption, and the dissolved medication in saliva must be swallowed for absorption in the proximal duodenum. Additionally, carbidopa/L-dopa is available in an oral capsule formulation containing immediate-release (IR) and extended-release (ER) beads (ie, Rytary) which can be sprinkled on food (eg, apple sauce).

Pharmacokinetics

There is marked intra- and intersubject variability in the time to peak plasma concentrations after oral carbidopa/L-dopa. This may in part be attributed to differences in gastric emptying as L-dopa is absorbed in the proximal duodenum by a saturable large neutral amino acid transport system.[48] Therefore, competition for this transporter by large dietary, or pharmaceutical, neutral amino acids (eg, leucine, phenylalanine) may result in reduced L-dopa bioavailability. However, for patients with early PD, this interaction is generally not significant.

L-Dopa is not bound to plasma proteins and is actively transported across the blood–brain barrier by the large neutral amino acid transporter system. In advanced PD, special diets involving protein restriction may improve L-dopa responsiveness and are sometimes implemented. A metabolite of L-dopa, 3-*O*-methyldopa also competes for transport, but it is not clear how this affects L-dopa clinical response.

When peripheral decarboxylation of L-dopa is inhibited by carbidopa, 3-*O*-methylation (via COMT) becomes the predominant catabolic pathway. The elimination half-life of L-dopa is about 1 hour, and this is extended to about 1.5 hours with the addition of carbidopa. With the addition of a COMT inhibitor such as entacapone to carbidopa/L-dopa, the elimination half-life is extended to about 2 to 2.5 hours.

The controlled-release (ie, Sinemet CR) and IR/ER carbidopa/L-dopa formulations (ie, Rytary) are 70% and 75% bioavailable, respectively, compared to standard IR carbidopa/L-dopa.[49] Manufacturer-provided dosage conversion recommendations are available to guide dosing conversions between carbidopa/L-dopa formulations.

Motor Complications of L-Dopa

7 Long-term L-dopa therapy is associated with a variety of motor complications, of which end-of-dose "wearing off" (motor fluctuations) and L-dopa peak-dose dyskinesias are the two most encountered.[50] These motor complications can become disabling and a challenge to manage. Risk factors associated with the development of motor complications include higher dosages of L-dopa and a younger age of PD onset.[51,52] The 5-year cumulative incidence of motor complications is about 50% in a medication naïve population.[53] Table 78-6 lists the common motor complications associated with long-term treatment with L-dopa and suggested initial management strategies. Initiating therapy with the controlled release (CR) form of carbidopa/L-dopa (ie, Sinemet CR) does not reduce the development of motor complications compared with IR carbidopa/L-dopa.[28]

TABLE 78-6

Common Motor Complications and Possible Initial Treatments

Effects	Possible Treatments
End-of-dose "wearing off" (motor fluctuation)	Increase frequency of carbidopa/L-dopa doses; add either COMT inhibitor or MAO-B inhibitor or dopamine agonist; add or switch to extended-release carbidopa/L-dopa (ie, Rytary); use L-dopa inhalation or apomorphine subcutaneous or sublingual
"Delayed on" or "no on" response	Give carbidopa/L-dopa on empty stomach; use carbidopa/L-dopa ODT; avoid carbidopa/L-dopa SR; use apomorphine subcutaneous or sublingual or L-dopa inhalation
Start hesitation ("freezing")	Increase carbidopa/L-dopa dose; add a dopamine agonist or MAO-B inhibitor; utilize physical therapy along with assistive walking devices or sensory cues (eg, rhythmic commands, stepping over objects)
Peak-dose dyskinesia	Provide smaller doses of carbidopa/L-dopa at the same or increased dosing frequency; reduce dose of adjunctive dopamine agonist; add amantadine

COMT, catechol-*O*-methyltransferase; MAO, monoamine oxidase; ODT, orally disintegrating tablet; SR, sustained release.

End-of-Dose "Wearing Off"

7 The terms "off" and "on" refer to periods of poor movement (ie, return of tremor, rigidity, or slowness) and good movement, respectively. End-of-dose "wearing off" prior to the next dose of medication is a common type of response fluctuation. This phenomenon is related to the increasing loss of neuronal storage capability for dopamine as well as the short half-life of L-dopa.[54] Initially, exogenous L-dopa is taken up by the remaining SNc neurons, converted to dopamine and stored in synaptic vesicles. With progressive loss of SNc neurons and storage capacity, patients become more dependent on exogenous carbidopa/L-dopa. Hence, the peripheral pharmacokinetic properties of L-dopa increasingly become the determinant of central dopamine synthesis. With advancing PD, the duration of action of a single carbidopa/L-dopa dose progressively shortens and in some cases may produce benefits for as little as 1 hour. As a result, carbidopa/L-dopa needs to be given more frequently, although other options are also available (see Table 78-6). In particular, the addition of the COMT inhibitor entacapone or an MAO-B inhibitor (ie, rasagiline, safinamide), or zonisamide (off-label use in the United States) extends the action of L-dopa and should be considered.[28] A dopamine agonist (eg, pramipexole, ropinirole, or rotigotine) can also be added to a carbidopa/L-dopa regimen for the management of "wearing off." The older CR L-dopa product (ie, Sinemet CR) has been investigated for the management of motor fluctuations, but the evidence is not compelling.[28] A newer IR/ER carbidopa/L-dopa formulation (ie, Rytary) contains beads that dissolve at different rates. Following administration, therapeutic L-dopa levels are rapidly achieved and are maintained for 4 to 5 hours providing efficacy for the management of motor fluctuations.[55] Clinical trials are currently underway investigating another IR/ER carbidopa/L-dopa formulation, which aims to further a steadier L-dopa level.[56]

Carbidopa/L-dopa enteral suspension is effective and safe for patients with advanced PD experiencing persistent, on/off fluctuations.[57] This enteral suspension is contained within a medication cassette reservoir and infusion into the small intestine is achieved by a portable pump device which requires placement of a percutaneous endoscopic gastrostomy tube along with a jejunal extension, through the abdominal wall. The medication infusion typically runs for 16 continuous hours per day and is turned off at night.

Less-invasive deliveries of carbidopa/L-dopa to minimize motor fluctuations are currently being investigated in clinical trials. ND0612 is a self-administered subcutaneous infusion of carbidopa/L-dopa currently in phase III trials. ABBV-951 is another subcutaneous infusion of carbidopa/L-dopa also in phase III clinical trials.[58]

For rapid relief of acute off episodes, apomorphine (available as either a subcutaneously or sublingually administered short-acting dopamine agonist) or a L-dopa dry powder for inhalation may be administered as needed.[59,60] Although not commonly performed, sipping small amounts of carbidopa/L-dopa solution frequently throughout the day is also a method for managing on/off fluctuations. A solution that is stable for 72 hours at room temperature can be prepared by adding 10 crushed tablets of carbidopa/L-dopa 10/100 (or 25/100) mg and 2 g crystalline ascorbic acid to 1 L of water.[61]

Often though, off episodes occur during the night, and patients will awaken in an off state because of an overnight decline of medication levels. Therefore, bedtime administration of a dopamine agonist or a medication formulation that provides sustained medication levels overnight (eg, carbidopa/L-dopa CR or IR/ER, ropinirole XL, pramipexole ER, rotigotine transdermal patch) can help reduce nocturnal off episodes and improve functioning upon awakening.

Nonadherence to medications also contributes to the frequency of off episodes. Therefore, engaging and supporting patients and caregivers in overcoming barriers to medication adherence is important.

"Delayed-On" or "No-On" Response

"Delayed-on" or "no-on" responses describe a delayed or absent onset of medication effect to individual doses of carbidopa/L-dopa which can be a result of delayed gastric emptying or decreased duodenum absorption. To overcome this effect, chewing a tablet or crushing it and then drinking a full glass of water or using the ODT formulation on an empty stomach can help mitigate effects of delayed gastric emptying. Alternatively, the use of the inhaled L-dopa bypasses the gastrointestinal (GI) tract to provide systemic absorption and help induce "on" time for patients.[62] Additionally, subcutaneously or sublingually administered apomorphine may be used as on-demand therapy for delayed-on or no-on periods.[62]

Freezing

"Freezing," or a sudden, episodic akinesia (lack of movement) of the lower extremities, is an event described by patients as a feeling where their "feet suddenly feel stuck to the floor" during ambulation or they have difficulty initiating steps (start hesitation) or turns (turn hesitation). As freezing often is exacerbated by anxiety or when perceived obstacles (eg, doorways, turnstiles) are encountered, this event may interfere with ambulation and increase the risk of falls. In addition to optimal pharmacological management, physical therapy and use of assistive walking devices and sensory cues aid in the reduction of "freezing" episodes.[63]

Dykinesias

9 Another complication of L-dopa therapy is "on" period dyskinesias that are involuntary choreiform movements usually involving the neck, trunk, and lower/upper extremities. Dyskinesias are specific to L-dopa therapy and if patients report "shakiness," it is important to clarify if they are referring to tremor or dyskinesias. To help differentiate the two, it is important to note that dyskinesias are usually associated with peak striatal dopamine levels (peak-dose dyskinesia) and, simplistically, can be thought of as too much movement secondary to extension of the L-dopa pharmacologic effect.[64] Lowering the dose of carbidopa/L-dopa to counteract dyskinesias should be attempted. However, the use of a lower dose may result in suboptimal control of parkinsonian features; thus, necessitating addition of another antiparkinsonian agent (eg, dopamine agonist). Another strategy is to lower the individual dose of L-dopa, but administer more frequently. Glutamate overactivity may also be involved, as suggested by the dyskinesia improvement observed with amantadine (NMDA-receptor antagonist) and other antiglutamate ligands.[65] Less commonly, dyskinesias also can develop during the rise and fall of L-dopa effects (the dyskinesia–improvement–dyskinesia or diphasic pattern of response). For severe dyskinesias (despite pharmacologically optimized therapy), surgery should be considered.

"Off-Period" Dystonia

In PD, dystonias are sustained muscle contractions that can occur and more commonly affect a distal lower extremity (eg, clenching of toes or involuntary turning of a foot). Dystonias often occur in the early morning hours, due to waning medication levels, and improve with the first carbidopa/L-dopa dose of the day. Remedies for early morning dystonia include bedtime administration of a long-acting dopamine agonist, long-acting carbidopa/L-dopa, or baclofen. Additionally, focal injections of botulinum toxin type A or B are effective for persistent focal dystonias, which can

also occur as L-dopa peak dose effect; therefore, additional management of this specific adverse event is similar to that of dyskinesias.[66]

Adenosine Receptor Antagonist

One of the newest FDA-approved agents for the adjunctive treatment of PD is the xanthine derivative, istradefylline, an adenosine A2AR antagonist. This non-dopaminergic medication is theorized to exert its effect by antagonizing the adenosine A2AR in the indirect movement pathway.[16] Patients with PD have been found to have an increase in adenosine A2ARs.[67] Adenosine increases the activation of the indirect pathway, further inhibiting movement. Antagonizing the A2AR therefore allows for decreased activation of the indirect pathway and may allow for an increase in movement.

Istradefylline is currently approved as an adjunctive treatment to L-dopa for patients with "off" episodes. It is generally well tolerated with the most common adverse effects including insomnia, hallucination, nausea, and constipation. The pharmacokinetics of istradefylline include metabolism primarily by cytochrome P450 (CYP450) CYP1A1 and CYP3A4 with an elimination half-life of approximately 80 hours.[68] It is recommended to avoid use in the presence of a strong CYP3A4 inducer and to reduce the dose when co-administered with a strong CYP3A4 inhibitor. The recommended starting dose is 20 mg daily, which can be increased to 40 mg daily. In patients who smoke more than 20 cigarettes a day (or equivalent tobacco product), the recommended dose is 40 mg per day.[68]

Monoamine Oxidase B Inhibitors

5 Three selective MAO-B inhibitors (rasagiline, safinamide, selegiline) are available for management of PD (see Table 78-3). The selective inhibition of MAO-B in the brain interferes with the degradation of dopamine and results in prolonged dopaminergic activity. Rasagiline and selegiline contain a propargylamine moiety, which is essential for conferring irreversible inhibition of MAO-B, in contrast to safinamide, which is a reversible MAO-B inhibitor.[69] At therapeutic doses, all three agents preferentially inhibit MAO-B over MAO-A.

A common concern with use of these agents is the potential for interactions with medications that possess serotonergic activity. Concomitant use of MAO-B inhibitors with meperidine and other selected opioid analgesics is contraindicated because of a small risk of serotonin syndrome. However, serotonergic antidepressants can be used concomitantly when clinically warranted, as these are not contraindicated.[70]

MAO-B inhibitors have also been investigated for neuroprotective properties (clinically referred to as *disease modification*). MAO-B inhibitors possess antiapoptotic properties, and MAO-B inhibition diverts dopamine degradation to an alternate route (ie, COMT) that does not generate free radicals (see Figs. 76-1 and 76-5).[71] To date, clinical studies to demonstrate disease modification with MAO-B inhibitors have yielded inconclusive results.[72-74]

5 8 Selegiline, also known as L-deprenyl, is marketed for extending L-dopa effects and is typically administered 5 mg twice daily. Selegiline is also available as an ODT formulation administered 1.25 to 2.5 mg once daily, and a transdermal formulation which is not indicated for PD. As monotherapy in early PD, selegiline provides modest improvements in motor function.[74] In advanced PD, adjunctive use of selegiline can provide up to 1 hour of extra "on" time for patients with "wearing off," although the data are inconsistent,[28] which may be explained, in part, by the poor and erratic bioavailability of selegiline.

As an amphetamine pharmacophore, selegiline undergoes first-pass hepatic metabolism, predominantly via CYP2B6 and 2C19, to end products of L-methamphetamine and L-amphetamine.[75] Adverse effects of selegiline are minimal but can include agitation, insomnia (especially if administered at bedtime), hallucinations, and orthostatic hypotension (see Table 78-4). Selegiline also increases the peak effects of L-dopa and can worsen pre-existing dyskinesias or psychiatric symptoms such as delusions. With the selegiline ODT formulation, first-pass hepatic metabolism is bypassed as a consequence of transmucosal absorption; hence, bioavailability is improved and formation of amphetamine metabolites is reduced.

5 8 Rasagiline is a second-generation, irreversible, selective MAO-B inhibitor administered at 0.5 or 1 mg once daily, which is effective as monotherapy in early PD. It is also effective as add-on therapy for managing motor fluctuations in advanced PD with efficacy similar to that of entacapone, offering approximately 1 hour of extra "on" time during the day.[28] Rasagiline is well tolerated with minimal GI or neuropsychiatric adverse effects and is metabolized by CYP1A2 to aminoindan, which is inactive and devoid of amphetamine-like properties.[76]

5 8 Safinamide is a reversible, selective MAO-B inhibitor administered at 50 or 100 mg once daily indicated as add-on therapy to carbidopa/L-dopa

for managing motor fluctuations and provides up to 1 hour of extra "on" time during the day.[28] Nondopaminergic effects include state-dependent inhibition of voltage-gated sodium channels and modulation of release of glutamate.[77] However, the extent to which these properties of safinamide contribute to the overall medication effect is unclear. Safinamide is well tolerated with minimal GI or neuropsychiatric adverse effects and is predominantly metabolized by nonmicrosomal enzymes (cytosolic amidases) to inactive metabolites which are excreted renally.[77]

Catechol-*O*-Methyltransferase Inhibitors

8 Three COMT inhibitors, entacapone, opicapone, and tolcapone, have been developed to extend the effects of L-dopa and are indicated for managing "wearing off". Mechanistically, all reduce the peripheral conversion of L-dopa to dopamine, thus enhancing central L-dopa bioavailability. Consequently, in the absence of L-dopa, they have no effect on PD symptoms. COMT inhibitors increase L-dopa area under the curve by approximately 35% and, for patients with "wearing off," can increase "on" time by about 1 to 2 hours.[28,78]

Tolcapone inhibits both peripheral and central COMT, but its use is limited by reports of fatal hepatotoxicity, such that strict monitoring of hepatic function, especially during the first 6 months of therapy, is required (see Table 78-4). Because of this risk, it is reserved for patients with fluctuations that are not responding to other therapies.[79]

Entacapone has a shorter half-life than tolcapone, and 200 mg needs to be given with each dose of carbidopa/L-dopa up to a maximum of eight times per day. A triple-combination product of carbidopa/L-dopa/entacapone offers convenience for some patients (ie, fewer tablets to administer). Unlike tolcapone, entacapone is not associated with hepatotoxicity; therefore, it is considered efficacious and clinically useful as adjunctive therapy to manage motor fluctuations.[28]

Opicapone is a third-generation COMT inhibitor that selectively blocks the peripheral conversion of L-dopa. Its long duration of action compared to entacapone and tolcapone allows for once-a-day dosing.[80] Opicapone 50 mg once daily at bedtime is the recommended dose for most patients and 25 mg daily for patients with moderate hepatic impairment. The mean "off" time reduction in clinical trials for opicapone has been greater than that for entacapone, suggesting a more robust clinical response.[81]

With all agents, augmentation of dopaminergic adverse effects may occur and generally are manageable by reduction of the carbidopa/L-dopa dosage. Patients should be advised that other adverse effects include brownish-orange urinary discoloration and diarrhea occurring weeks to months after treatment initiation may occur with the use of entacapone or tolcapone.

Dopamine Agonists

Dopamine agonists fall into two pharmacologic subtypes: ergot-derived agonists (bromocriptine) and the non-ergot agonists (apomorphine, pramipexole, ropinirole, and rotigotine).[82] Non-ergot agonists have a better safety profile and are more commonly used than the ergot-derived agonists. Pharmacologically dopamine agonists stimulate dopamine receptors (eg, D_1, D_2, D_3) and are useful as monotherapy in mild-to-moderate PD and also as adjuncts to carbidopa/L-dopa therapy to reduce "off" time in patients with motor fluctuations.[28]

10 Compared with long-term carbidopa/L-dopa therapy, dopamine agonist significantly reduce the risk of developing motor complications.[83,84] For younger patients, who are more likely to develop motor complications, dopamine agonists are preferred over carbidopa/L-dopa. For older patients, dopamine agonists should be used conservatively due to greater likelihood for the development of intolerable adverse effects and for patients with cognitive problems or dementia, dopamine agonists should be avoided.

Common adverse effects of dopamine agonists include nausea, confusion, drowsiness, hallucinations, lower-extremity edema, and orthostatic hypotension (see Table 78-4).[85] When initiating therapy, a slow dose titration is required to minimize development of adverse effects, particularly nausea. The addition of a dopamine agonist to carbidopa/L-dopa therapy also can induce dyskinesias, especially in patients with pre-existing dyskinesias. Less common but serious adverse effects include impulsive and compulsive behaviors (eg, pathologic gambling or shopping; paraphilia), delusions/psychosis, and sleep attacks (sudden, unexpected episodes of sleep). Hallucinations and delusion should be managed using a systematic approach that starts with dose reduction or discontinuation of the dopamine agonist, and if needed, addition of a second-generation antipsychotic

medication such as clozapine, pimavanserin, or quetiapine.[24,30,86] Of these, only pimavanserin is FDA-approved for psychosis in PD. Involvement of caregivers in surveillance for potential adverse effects of dopamine agonists, particularly development of delusions, hallucinations, and impulsive behaviors, facilitates earlier detection and management.

Apomorphine is an aporphine alkaloid originally derived from morphine that lacks narcotic properties.[59] It exhibits poor oral bioavailability due to extensive hepatic first-pass metabolism and is administered either sublingually or subcutaneously. Apomorphine is indicated for patients with advanced PD who are experiencing intermittent "off" episodes despite optimized therapy. Upon subcutaneous administration, apomorphine produces an "on" response within 20 minutes. The effective dose ranges from 2 to 6 mg per injection. Sites of injection (abdomen, upper arm, and upper thigh) should be rotated to avoid development of subcutaneous nodules. The elimination half-life for subcutaneous apomorphine is approximately 40 minutes, and the duration of benefit can be up to 100 minutes.[87] In comparison, the sublingual dosage form of apomorphine typically takes about 30 to 60 minutes to produce therapeutic effects and benefits can last up to 90 minutes.[88,89] Patients may take anywhere from 10 to 30 mg per dose, not to exceed five treatments per day. The half-life for the sublingual formulation is about 90 minutes. Nausea and vomiting are common adverse effects for both formulations, and prior to the initiation of apomorphine, patients should be premedicated with the antiemetic, trimethobenzamide. Of note, apomorphine delivered continuously via a subcutaneous infusion for patients with advanced PD and motor fluctuations is currently being studied in clinical trials in the United States. This delivery of apomorphine is currently an approved therapy in Europe.[90]

Pramipexole is initiated at a dose of 0.125 mg three times a day and increased every 5 to 7 days, as tolerated, to a maximum of 1.5 mg three times a day.[91] An extended-release pramipexole formulation is also available. Immediate-release ropinirole is initiated at 0.25 mg three times a day and increased by 0.25 mg three times a day on a weekly basis to a maximum of 24 mg/day.[92] An extended-release ropinirole formulation also is available. Pramipexole is renally excreted with an 8- to 12-hour half-life. The initial dosage must be adjusted in renal insufficiency (0.125 mg twice daily for creatinine clearances of 35-59 mL/min [0.58-0.99 mL/s], 0.125 mg once daily for creatinine clearances of 15-34 mL/min [0.25-0.57 mL/s]).[91]

Ropinirole has a 6-hour half-life and is metabolized by CYP1A2; therefore, potent inhibitors (eg, fluoroquinolone antibiotics) and inducers (eg, cigarette smoking) of this enzyme likely will lead to alterations in its clearance.[92]

Rotigotine transdermal patch is initiated at 2 mg once daily and increased weekly by 2 mg increments to achieve the desired therapeutic effect. The rotigotine transdermal patch provides continuous release of medication over a 24-hour period.[93] The patch application sites should be rotated to minimize skin irritation and rash. Rotigotine disposition is not affected by hepatic or renal impairment, and CYP-mediated interactions are not significant.

EVALUATION OF THERAPEUTIC OUTCOMES

1 Comprehensive medication management with optimization of medications related to PD improves patient outcomes.[94-97] Routine evaluation and monitoring of motor and nonmotor symptoms should occur every 3 to 6 months for patients on a stable treatment regimen. With the changes in pharmacotherapy (eg, medication addition, discontinuation, dose change), follow-up monitoring for efficacy and adverse effects should occur within 1 or 2 weeks and may occur via telephone.[98] Table 78-7 lists the monitoring parameters for PD therapy. Patient and caregiver satisfaction is an important component of evaluating therapeutic outcomes. Toward this end, establishing appropriate treatment expectations is important. Patients and caregivers should be educated that symptoms of PD often progresses with time, and adjustments to the medication regimen will be required to manage motor and nonmotor features. Additionally, some symptoms do not respond to pharmacotherapy (eg, freezing, gait, and postural instability). Assessment of the patient's general level of functioning, including activities of daily living and mobility, is important to determine when medication adjustments or physical therapy interventions are needed. It is also important to be aware of and adhere to the general guidelines and recommendations for geriatric health maintenance and disease prevention (eg, bone health, routine vaccinations, and vitamin and mineral supplementations).

TABLE 78-7

Monitoring Parkinson Disease Therapy

1. Monitor medication administration times. Educate the patient that immediate-release carbidopa/L-dopa is absorbed best on an empty stomach but is commonly taken with food (preferably nonprotein snack) to minimize nausea. Avoid administration of conventional selegiline in the late afternoon or evening to minimize insomnia.
2. Monitor to ensure that the patient and/or caregivers understand the prescribed medication regimen. For example, they should understand that catechol-*O*-methyltransferase inhibitors work by enhancing the effect of L-dopa and that the patient should not discontinue medication without notifying the clinician.
3. Monitor and inquire specifically about dose-by-dose effects of medication, including response to doses of medication and the presence of dyskinesias, "wearing-off" effects, dizziness, nausea, orthostasis, or visual hallucinations. Offer suggestions to help alleviate these or encourage the patient to discuss them with the clinician.
4. Monitor caregiver involvement and facilitation for early detection of abnormal behaviors, dyskinesias, falls, hallucinations, impulsivity, memory problems, mood changes, and sleep disorders.
5. Monitor for nonadherence and, if present, inquire for possible reasons (eg, dosing convenience, financial issues, and adverse effects) and offer suggestions.
6. Monitor for presence of medications that can exacerbate idiopathic Parkinson disease motor features (eg, D_2-receptor blockers).
7. Monitor for presence of medications that can exacerbate nonmotor symptoms. Evaluate whether the presence of an anticholinergic agent is causing confusion or cognitive impairment.

Patients and caregivers can participate in treatment by recording medication administration times as well as the duration of "on and off" times that can be reviewed at each visit. Periodic review of all prescription and nonprescription medications that the patient is taking should be performed to identify medication therapy problems such as the use of medications with adverse effects that can exacerbate PD motor and nonmotor features. For example, D_2 blockers (such as metoclopramide and firstgeneration antipsychotics) can worsen motor features and should be avoided. If the patient reports memory problems, medications with anticholinergic properties should be avoided.

Nonmotor symptoms must be identified, assessed, managed, and monitored. These include anxiety, cognitive impairment, constipation, daytime sleepiness, depression, dro oling, dysphagia, fatigue, falls, hallucinations/psychosis, impulsivity, insomnia, orthostatic hypotension, overactive bladder, pain, REM sleep behavior disorder, and restless legs syndrome. Screening for anxiety or depressive disorders will help determine if antidepressant or antianxiety therapy is needed.[99] If falling is a problem, it is important to investigate whether falls are secondary to insufficient motor control, orthostatic hypotension, or medication adverse effects, such as dizziness. The former may necessitate an increase in dose of antiparkinsonian agents, and the latter two conditions, a reduction in medication dosage. Physical therapy is also helpful for strengthening ambulation and balance skills to minimize falls. The patient should be questioned about any difficulties with their antiparkinsonian medications, including presence of adverse effects. Recommendations always should be made in view of the patient's perception of the severity of symptoms and effect on quality of life.

CONCLUSION

Despite many advances in neuroscience, a definitive cause of PD remains unknown. Each of the available therapies provide various degrees of symptomatic benefit, and the choice of agent is patient specific. The appropriate pharmacotherapy can significantly improve a patient's quality of life and functional status. The goal of management remains maintaining acceptable functional control with minimal treatment emergent motor and nonmotor complications. Thoughtful consideration for choice of initial and adjunctive therapy is critical for optimizing short- and long-term outcomes.

ABBREVIATIONS

COMT	catechol-*O*-methyltransferase
CR	controlled release
CYP450	cytochrome P450
D_1	dopamine receptor subtype 1
D_2	dopamine receptor subtype 2
DBS	deep-brain stimulation
ER	extended release
GABA	γ-aminobutyric acid
GI	gastrointestinal
GPi	globus pallidus interna
IR	immediate release
L-dopa	levodopa
MAO	monoamine oxidase
NMDA	*N*-methyl-D-aspartate
ODT	orally disintegrating tablet
PD	Parkinson disease
REM	rapid eye movement
SNc	substantia nigra pars compacta
SNr	substantia nigra pars reticulate
STN	subthalamic nucleus

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SELF-ASSESSMENT QUESTIONS

1. Parkinson disease (PD) is characterized by a nigrostriatal deficiency of

   A. Acetylcholine.

   B. Dopamine.

   C. Norepinephrine.

   D. Serotonin.

2. The clinical diagnosis of PD is based on the presence of bradykinesia and at least one of three other features: muscular rigidity, resting tremor, and/or

   A. Dystonia.

   B. Nystagmus.

   C. Postural instability.

   D. Seizures.

3. Which of the following is the most effective drug for PD?

   A. Amantadine

   B. Carbidopa/levodopa

C. Pramipexole

D. Rasagiline

4. An 80-year-old with newly diagnosed PD and a history of memory problems and confusion is best treated with

A. Amantadine.

B. Carbidopa/levodopa.

C. Trihexyphenidyl.

D. Ropinirole

5. The mechanism of action for entacapone is

A. COMT inhibition.

B. MAO-B inhibition.

C. D_2-receptor inhibition.

D. Dopa-decarboxylase inhibition.

6. Which of the following agents can worsen PD symptoms?

A. Haloperidol

B. Ondansetron

C. Pimavanserin

D. Rasagiline

7. A patient with PD is taking carbidopa/levodopa 25/100 mg three times a day and reports that they tend to slow down 2 hours before his next carbidopa/levodopa dose. This patient is most likely experiencing

A. Delayed-onset response

B. Dyskinesia

C. Freezing

D. “Wearing off”

8. A 70-year-old patient taking carbidopa/levodopa 25/100 mg three times a day for PD is experiencing end-of-dose “wearing off.” Carbidopa/levodopa is the only medication they take for PD and adherence is excellent. The best next step is to

A. Add tolcapone.

B. Consider surgery.

C. Add trihexyphenidyl.

D. Increase carbidopa/levodopa to four times daily.

9. A 63-year-old patient taking carbidopa/levodopa 25/100 mg four times a day for PD is experiencing end-of-dose “wearing off.” The patient would

like a medication that is only dosed once a day that may reduce this effect. The best recommendation is to

A. Add tolcapone.

B. Add entacapone.

C. Add opicapone.

D. Add inhaled levodopa.

10. A 72-year-old patient with moderate-to-severe PD was placed on carbidopa/levodopa 25/100 mg three times a day by his primary care physician. They are complaining of nausea and stomach upset since starting the medication. The best recommendation is to

A. Increase the carbidopa/levodopa dose by 50%.

B. Discontinue the medication and switch to rasagiline.

C. Discontinue the medication and switch to a ropinirole.

D. Recommend taking carbidopa/levodopa with a nonprotein snack.

11. A 71-year-old patient has had PD for 8 years and is currently taking pramipexole 1.5 mg three times a day and carbidopa/levodopa 25/100 mg four times a day. Their spouse claims that they are complaining of seeing spiders and bugs running across the floor and imaginary children in their house. The patient is diagnosed with PD psychosis. At this point, the best recommendation is to

A. Increase the pramipexole dose.

B. Reduce the pramipexole dose.

C. Increase the carbidopa/levodopa dose.

D. Reduce the carbidopa/levodopa dose.

12. A 65-year-old patient with PD is experiencing moderate dyskinesias that are bothersome. The patient is on carbidopa/levodopa 25/100 mg two tablets at 7 am and one tablet at 11 am, 2 pm, 5 pm, 8 pm, and 11 pm. Which of the following is most appropriate?

A. Add amantadine

B. Add entacapone

C. Add rasagiline

D. Add apomorphine

13. A 63-year-old patient with PD has done well on rasagiline 1 mg once a day and ropinirole 4 mg three times a day for several years. In the past, higher doses of ropinirole resulted in excessive drowsiness. They are not experiencing “wearing off” fluctuations or dyskinesias. Physical examination reveals clinically significant slowness and rigidity and the patient desires more symptom relief. At this point, the best recommendation would be to

A. Add carbidopa/levodopa.

B. Add entacapone.

C. Add pramipexole.

D. Consider DBS surgery.

14. You are educating a patient with PD on their new prescription for apomorphine. Which of the following should the patient be informed of as

common adverse effects?

A. High blood pressure

B. Dry mouth

C. Nausea

D. Livedo reticularis

15. A 74-year-old patient has had PD for 8 years and is currently taking carbidopa/levodopa 25/100 mg one and a half tablets five times a day. They are experiencing troublesome hallucinations. Previous attempts to lower the carbidopa/levodopa dose were not tolerated due to significant worsening of motor symptoms. The best recommendation is to add

A. Risperidone.

B. Haloperidol.

C. Pimavanserin.

D. Ropinirole.

SELF-ASSESSMENT QUESTION-ANSWERS

1. **B.** See Figs. 78-1 and 78-2. At the cellular level, degeneration of dopaminergic neurons resulting in a deficiency of dopamine within the nigrostriatal system is a hallmark of PD. In PD, deficiencies of acetylcholine, norepinephrine, and serotonin may occur in other parts of the brain.

2. **C.** See Table 78-1. The clinical diagnosis of PD requires the presence of bradykinesia and at least one of the following: resting tremor, rigidity, and/or postural instability. The concurrent presence of dystonia, nystagmus, or seizures would suggest an atypical form of parkinsonism.

3. **B.** Levodopa is the immediate precursor of dopamine and, in combination with a peripherally acting L-amino acid decarboxylase inhibitor (carbidopa or benserazide), remains the most effective drug for the symptomatic treatment of PD. Regardless of what the initial therapeutic agent is (eg, amantadine, dopamine agonist, or rasagiline) ultimately, all patients with PD will require levodopa.

4. **B.** See Table 78-4. Anticholinergic medications (eg, trihexyphenidyl) should be used with caution in older patients and in those with pre-existing cognitive difficulties due to anticholinergic adverse effects exacerbating confusion. Amantadine should be avoided as adverse effects include confusion and hallucinations with older patients being particularly prone to developing confusion. Dopamine agonists (eg, ropinirole) should also be avoided in the older patients especially those with preexisiting cognitive difficulties.

5. **A.** Entacapone is an inhibitor of catechol-*O*-methyltransferase (COMT). Examples of monoamine oxidase type-B (MAO-B) inhibitors are rasagiline, safinamide, and selegiline. An example of a dopa-decarboxylase inhibitor is carbidopa. Examples of medications that inhibit D_2 receptors include metoclopramide, prochlorperazine, and first-generation antipsychotics such as haloperidol.

6. **A.** Haloperidol blocks D_2 receptors and will worsen the motor symptoms of PD and is associated with medication-induced parkinsonism (see Table 78-1). Ondansetron is an antiemetic that works as a $5HT_3$ antagonist and is not implicated in worsening PD symptoms like the D_2 receptor blockers prochlorperazine and metoclopramide. Pimavanserin does not block D_2 receptors nor does rasagiline and both are FDA-indicated for the treatment of PD (pimavanserin for PD psychosis and rasagline for symptoms of PD) (Table 78-1).

7. **D.** End-of-dose “wearing off” is a common type of response fluctuation and is reported as the onset of “off” periods (or slowing down in movements) prior to the next dose of medication. “Delayed-on” or “no-on” responses describe a delayed or absent onset of drug effect to individual doses of carbidopa/levodopa. “Freezing” is a sudden, episodic akinesia of the lower extremities and described by patients as a feeling where their “feet suddenly feel stuck to the floor” during ambulation or they have difficulty initiating steps (start hesitation) or turns (turn hesitation). Freezing often is exacerbated by anxiety or when perceived obstacles (eg, doorways, turnstiles) are encountered. Dyskinesias are

involuntary choreiform movements involving usually the neck, trunk, and lower/upper extremities and usually associated with peak striatal dopamine levels (peak-dose dyskinesia) and, simplistically, can be thought of as too much movement secondary to extension of the levodopa pharmacologic effect. See "Carbidopa/L-Dopa" section.

8. **D.** With advancing PD, the duration of action of a single carbidopa/levodopa progressively shortens. As a result, carbidopa/levodopa needs to be given more frequently. Given that this patient has excellent adherence to carbidopa/levodopa, increasing the carbidopa/levodopa frequency to four times per day is the next best step prior to the addition of additional medications for "wearing-off" or consideration for surgery.

9. **C.** With advancing PD, the duration of action of a single carbidopa/levodopa progressively shortens. As a result, carbidopa/levodopa needs to be given more frequently or the addition of adjunctive medications for "wearing-off" must be considered. Opicapone is an inhibitor of catechol-*O*-methyltransferase (COMT) that is administered once daily to reduce motor fluctuations. Both tolcapone and entacapone are also COMT inhibitors, but require administration with each dose of carbidopa/levodopa. Inhaled levodopa may provide relief for "wearing off," but would likely require administration every time "wearing off" occurs, which in this case is four times a day.

10. **D.** See Tables 78-4 and 78-7. Nausea is a common adverse effect of carbidopa/levodopa and administration with food (preferably a nonprotein snack) is the first step in minimizing nausea. Increasing the carbidopa/levodopa dose by 50% will exacerbate the nausea and discontinuation of the carbidopa/levodopa is not appropriate at this stage.

11. **B.** See Table 78-2. Hallucinations and delusion should be managed using a systematic approach that starts with dose reduction or discontinuation of the dopamine agonist. Increasing the dose of antiparkinson medication will worsen the patient's symptoms of psychosis.

12. **A.** See Table 78-4. Amantadine is often used for management of levodopa-induced dyskinesia. The antidyskinetic properties of amantadine are presumed to be mediated by antiglutamate properties that, in the setting of dyskinesias, dominate over dopaminergic properties. The addition of entacapone, rasagiline, or apomorphine will likely worsen pre-existing dyskinesias.

13. **A.** Levodopa remains the most effective symptomatic medication and, regardless of what the initial therapeutic agents are; ultimately, all patients with PD will require levodopa. For this patient, the addition of carbidopa/levodopa would be the best recommendation. Addition of entacapone would be ineffective as the patient is not currently on carbidopa/levodopa. The addition of pramipexole (a dopamine agonist) is inappropriate because the patient is currently on ropinirole, which is also a dopamine agonist. Surgery is reserved for patients with fluctuations or dyskinesia that are not responding to other therapies. See "Pharmacologic Therapy" section.

14. **C.** See Table 78-4. Nausea is a common side effect of dopamine agonists. Apomorphonine requires close initial titration due to the risk of orthostatic hypotension, not high blood pressure. Dry mouth is an anticholinergic adverse effect of benztropine or trihexyphenidyl. Livedo reticularis is an adverse effect of amantadine.

15. **C.** See Table 78-2. Pimavanserin is FDA-approved for management of psychosis in PD. Risperidone and haloperidol are potent inhibitors of D_2 receptors and should be avoided due to risk of worsening motor symptoms of parkinsonism. Ropinirole is a dopamine agonist and will worsen pre-existing hallucinations/psychosis in patients with PD.