Chapter 57: Parkinson Disease

INTRODUCTION

- *Parkinson disease* (PD) has highly characteristic neuropathologic findings and a clinical presentation, including motor deficits and, in some cases, mental deterioration.

PATHOPHYSIOLOGY

- The true etiology of PD is unknown.
- Two hallmark features in the substantia nigra pars compacta are loss of neurons and presence of Lewy bodies. The degree of nigrostriatal dopamine loss correlates positively with severity of motor symptoms.
- Reduced activation of dopamine$_1$ and dopamine$_2$ receptors results in greater inhibition of the thalamus and reduced activation of the motor cortex. Clinical improvement may be tied to restoring activity more at the dopamine$_2$ receptor than at the dopamine$_1$ receptor.

CLINICAL PRESENTATION

- PD develops insidiously and progresses slowly over many years.

General Features

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

Motor Symptoms

- 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.
- 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 slow to a quickened pace), flexed posture, “freezing” at initiation of movement, hypomimia (reduced facial animation), hypophonia (reduced voice volume), and micrographia.

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.

DIAGNOSIS

- The clinical diagnosis of PD is based on the presence of bradykinesia and at least one of the three other features: muscular rigidity, resting tremor, and postural instability (**Table 57-1**).
- There are no laboratory tests available to diagnose PD, including genetic testing.
- Neuroimaging may be useful for excluding other diagnoses.
- Medication history should be obtained to rule out drug-induced parkinsonism.

TABLE 57-1

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")
- 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/levodopa
  - levodopa response for 5 years or longer
  - Presence of levodopa dyskinesias

Differential diagnosis

- Essential tremor
- Pharmacotoxicity (drug-induced)
  - Antiemetics (eg, metoclopramide, prochlorperazine)
  - Antipsychotics (eg, chlorpromazine, fluphenazine, haloperidol, olanzapine, risperidone, thioridazine)
  - Other drugs (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)

TREATMENT

- Goals of Treatment: The goals of treatment are to minimize symptoms, disability, and side effects while maintaining quality of life. Education of patients and caregivers, exercise, and proper nutrition are essential.
- To date, no treatments have been shown to effectively change the course of PD by slowing or halting its progression (disease modification).

Nonpharmacologic Therapy

- 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
- Other biotherapies, such as stem cell and gene-based approaches, are currently under investigation and remain highly experimental.

Pharmacologic Therapy

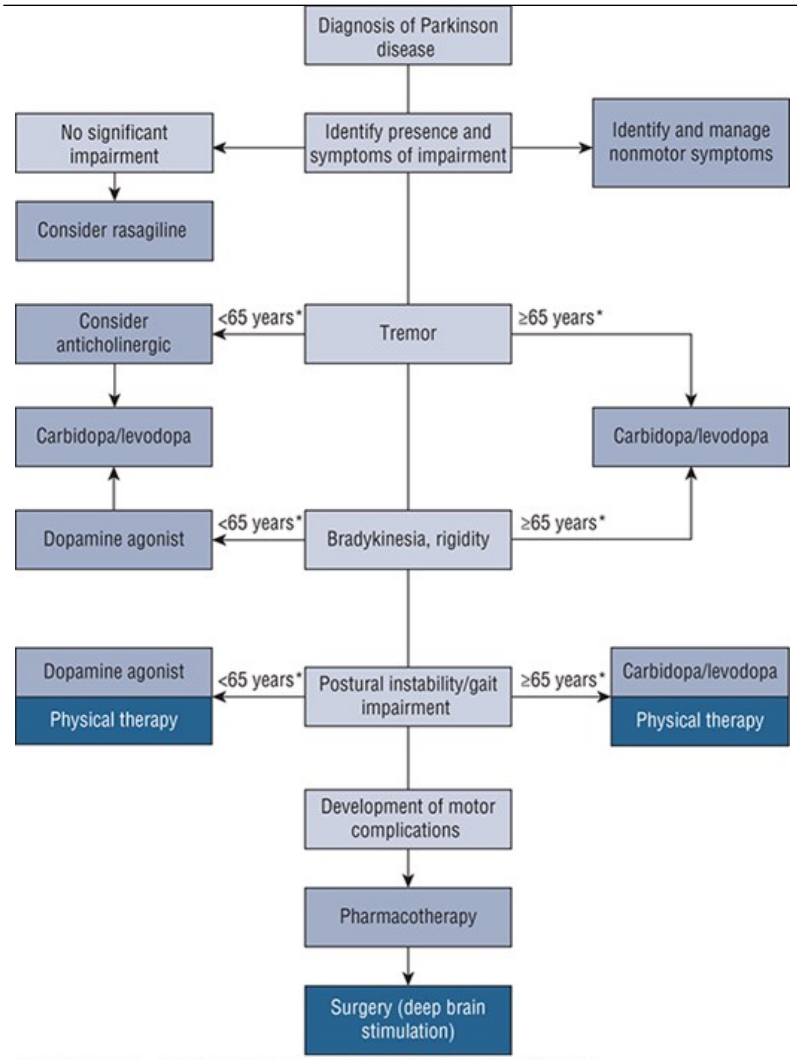
General Approach

- An algorithm for management of early to advanced PD is shown in **Figure 57-1**. **Table 57-2** is a summary of available antiparkinson medications and their dosing, and **Table 57-3** shows side effect monitoring.
- Initial monotherapy usually begins with a monoamine oxidase-B (MAO-B) inhibitor.
- Ultimately, all patients will require the use of **carbidopa/levodopa** either as monotherapy or in combination with other agents.
- With the development of motor fluctuations, patients should administer carbidopa/levodopa more frequently or addition of a COMT inhibitor, MAO-B inhibitor, or dopamine agonist to the carbidopa/levodopa regimen should be considered.
- For management of carbidopa/levodopa–induced peak-dose dyskinesias, a reduction in levodopa dose and/or addition of amantadine should be considered.

FIGURE 57-1

General approach to the management of early to advanced Parkinson disease.

Age is not the sole determinant for drug choice. Other factors such as cognitive function and overall tolerability of drug (especially in older patients) should be considered.



Source: Terry L. Schwinghammer, Joseph T. DiPiro, Vicki L. Ellingrod, Cecily V. DiPiro: *Pharmacotherapy Handbook, 11e*

TABLE 57-2

Dosing of Drugs Used in Parkinson Disease[a]

Generic Name	Trade Name	Starting Dose[b] (mg/day)	Maintenance Dose[b] (mg/day)	Dosage Forms (mg)
Anticholinergic drugs				
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/levodopa	Sinemet	300[c]	300–2000[c]	10/100, 25/100, 25/250
Carbidopa/levodopa ODT	Parcopa	300[c]	300–2000[c]	10/100, 25/100, 25/250

Carbidopa/levodopa CR	Sinemet CR	400[c]	400–2000[c]	25/100, 50/200
Carbidopa/levodopa IR/ER	Rytary	435[c]	435–2450[c]	23.75/95, 36.25/145, 48.75/195, 61.25/245[d]
Carbidopa/levodopa enteral suspension	Duopa	1000[c]	1000–2000[c]	4.63/20 per mL
Carbidopa/levodopa/entacapone	Stalevo	600[e]	600–1600[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]
Bromocriptine	Parlodel	2.5–5	15–40	2.5, 5
Pramipexole	Mirapex	0.125	1.5–4.5	0.125, 0.25, 0.5, 1, 1.5
Pramipexole ER	Mirapex ER	0.375	1.5–4.5	0.375, 0.75, 1.5, 3, 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	200–1600	200
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

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

[b]Dosages may vary.

[c]Dosages expressed as levodopa component.

[d]Dosages of Rytary were developed to avoid confusion with other oral carbidopa/levodopa products that contain levodopa 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.

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

TABLE 57-3

Monitoring of Potential Adverse Reactions to Drug Therapy for Parkinson Disease

Generic Name	Adverse Drug Reaction	Monitoring Parameter	Comments
Amantadine	Confusion	Mental status; renal function	Reduce dosage; adjust dose for renal impairment
	Livedo reticularis	Lower extremity examination; ankle edema	Reversible upon drug 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/levodopa	Drowsiness Dyskinesias Nausea	Mental status Abnormal involuntary movements Nausea	Reduce dose Reduce dose; add amantadine Take with food (eg, nonprotein snack)
COMT inhibitors			
Entacapone	Augmentation of levodopa side effects; also diarrhea	See carbidopa/levodopa; also bowel movements	Reduce dose of levodopa; antidiarrheal agents

Tolcapone	See entacapone; also liver toxicity	See carbidopa/levodopa; also ALT/AST	See carbidopa/levodopa; 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 Impulsivity Nausea Orthostatic hypotension	Mental status Mental status Lower extremity swelling Behavior, mental status Behavior Nausea Blood pressure, dizziness upon standing	Reduce dose Reduce dose Reduce dose or discontinue medication Reduce dose or discontinue medication Discontinue medication Titrate dose upward slowly; take with food Reduce dose
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
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.

Anticholinergic Medications

- Anticholinergic drugs can improve tremor and sometimes dystonic features in some patients, but they rarely substantially improve bradykinesia

or other disabilities. They can be used as monotherapy or in conjunction with other antiparkinson drugs.

- Anticholinergic side effects include dry mouth, blurred vision, constipation, and urinary retention. More serious reactions include forgetfulness, confusion, sedation, depression, and anxiety (see **Table 57-3**). Patients with preexisting cognitive deficits and the elderly are at greater risk for central anticholinergic side effects.

Amantadine

- Amantadine often provides modest benefit for tremor, rigidity, and bradykinesia, but is most often used for levodopa-induced dyskinesia.
- Doses should be reduced in patients with renal dysfunction (100 mg/day with creatinine clearances of 30–50 mL/min [0.50–0.84 mL/sec], 100 mg every other day for creatinine clearances of 15–29 mL/min [0.25–0.49 mL/sec], and 200 mg every 7 days for creatinine clearances less than 15 mL/min [0.25 mL/sec]) and those on hemodialysis.
- Adverse effects include sedation, dry mouth, hallucinations, dizziness, and confusion. Livedo reticularis (a diffuse mottling of the skin in the upper or lower extremities) is a common but reversible side effect.

Levodopa and Carbidopa/Levodopa

- **Levodopa** is the immediate precursor of dopamine and, in combination with a peripherally acting L-amino acid decarboxylase (L-AAD) inhibitor (carbidopa or benserazide), remains the most effective drug for the symptomatic treatment of PD.
- In the central nervous system (CNS) and peripherally, levodopa is converted by L-AAD to dopamine. In the periphery, carbidopa or benserazide can block L-AAD, thus increasing CNS penetration of administered levodopa and decreasing dopamine adverse effects (eg, nausea, cardiac arrhythmias, postural hypotension, and vivid dreams). Benserazide is unavailable in the United States.
- The usual maximal dose of levodopa tolerated is approximately 1000 to 1500 mg/day.
- About 75 mg of carbidopa is required to effectively block peripheral L-AAD, but some patients need more. Carbidopa/levodopa 25/100 mg tablet three times daily is the usual initial maintenance dose. Also available are the 25/250 mg and 10/100 mg dosage forms. Controlled-release preparations of carbidopa/levodopa are also available (**Table 57-2**). For patients with difficulty swallowing, an orally disintegrating tablet is available, and a capsule containing beads is available which can be sprinkled on food (Rytary).
- After oral levodopa administration, time to peak plasma concentrations varies intra- and intersubject. Meals delay gastric emptying, but antacids promote gastric emptying. Levodopa is absorbed primarily in the proximal duodenum via a saturable large neutral amino acid transport system, thus high-protein meals can interfere with bioavailability.
- Levodopa is not bound to plasma proteins, and the elimination half-life is approximately 1 hour. Adding carbidopa or benserazide can extend the half-life to 1.5 hours, and adding a COMT inhibitor (eg, **entacapone**) can extend it to approximately 2–2.5 hours.
- Sinemet CR and Rytary are 70% and 75% bioavailable compared to the standard immediate release carbidopa/levodopa formulation.

  ✔ Long-term, levodopa-associated motor complications can be disabling. The most common of these are “end-of-dose wearing off” and “peak-dose dyskinesias.” The risk of developing motor fluctuations or dyskinesias is approximately 10% per year of levodopa therapy. However, motor complications can occur 5–6 months after starting levodopa, especially when excessive doses are used initially. **Table 57-4** shows these motor complications and suggests management strategies.

  ✔ End-of-dose “wearing off” is related to the increasing loss of neuronal dopamine storage capability and the short half-life of levodopa. Bedtime administration of a dopamine agonist or a drug formulation that provides sustained drug levels overnight (eg, carbidopa/levodopa CR or IR/ER, ropinirole XL, pramipexole ER, rotigotine transdermal patch) can help reduce nocturnal off episodes and improve functioning upon awakening. Administration of Rytary may also be useful, as therapeutic levels of levodopa are rapidly achieved and maintained for 4–5 hours (see **Table 57-4**).

  ✔ “Delayed-on” or “no-on” can result from delayed gastric emptying or decreased absorption in the duodenum. Chewing or crushing

carbidopa/levodopa tablets and taking with a glass of water or using the orally disintegrating tablet on an empty stomach may help. Subcutaneous **apomorphine** may be used as rescue therapy.

✔ "Freezing," an episodic inhibition of lower extremity motor function, may be worsened by anxiety and may increase falls.

✔ Dyskinesias, involuntary choreiform movements usually involving the neck, trunk, and extremities, are usually associated with peak striatal dopamine levels. Less commonly, dyskinesias can develop during the rise and fall of levodopa effects (the dyskinesias-improvement-dyskinesias or diphasic pattern of response).

✔ "Off-period" dystonia muscle contractions occur most commonly in distal lower extremities (eg, feet or toes), often in the early morning. Consider bedtime administration of sustained-release products, use of **baclofen**, or selective denervation with **botulinum toxin**. If dystonia occurs as part of an levodopa peak dose effect, management is similar to that of dyskinesias.

TABLE 57-4

Common Motor Complications and Possible Initial Treatments

Effects	Possible Treatments
End-of-dose "wearing off" (motor fluctuation)	Increase frequency of carbidopa/levodopa doses; add either COMT inhibitor or MAO-B inhibitor or dopamine agonist; add or switch to extended-release carbidopa/levodopa (ie, Rytary); use levodopa inhalation
"Delayed on" or "no on" response	Give carbidopa/levodopa on empty stomach; use carbidopa/levodopa ODT; avoid carbidopa/levodopa SR; use apomorphine subcutaneous or levodopa inhalation
Start hesitation ("freezing")	Increase carbidopa/levodopa 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/levodopa; reduce dose of adjunctive dopamine agonist; add amantadine

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

Monoamine Oxidase B Inhibitors

- Three selective MAO-B inhibitors (**rasagiline, safinamide, selegiline**) are available for management of PD.
- Rasagiline and selegiline contain a propargylamine moiety, which is essential for conferring irreversible ("suicide") inhibition of MAO-B, in contrast to safinamide, which is a reversible MAO-B inhibitor. At therapeutic doses, all three agents preferentially inhibit MAO-B over MAO-A.
- Concomitant use of MAO-B inhibitors with meperidine and other selected opioid analgesics is contraindicated due to the small risk of serotonin syndrome. However, drugs with serotonergic antidepressants can be used concomitantly when clinically warranted.
- As monotherapy in early PD, both selegiline and rasagiline provide modest improvements in motor function.
- As add-on therapy, all three MAO-B inhibitors can provide up to 1 hour of extra "on" time for patients
- Selegiline also increases the peak effects of levodopa and can worsen preexisting dyskinesias or psychiatric symptoms, such as delusions. Metabolites of selegiline are L-methamphetamine and L-amphetamine. The oral disintegrating tablet may provide improved response and fewer side effects than the conventional formulation.
- Both rasagiline and safinamide are well tolerated with minimal GI or neuropsychiatric side effects

Catechol-*O*-Methyltransferase Inhibitors

- **Tolcapone** and **entacapone** are used in conjunction with carbidopa/levodopa to prevent the peripheral conversion of levodopa to dopamine (increasing the area under the curve of levodopa by approximately 35%). Thus, "on" time is increased by approximately 1–2 hours, and dosage requirements of levodopa are decreased. Avoid concomitant use of nonselective MAO inhibitors to prevent inhibition of the pathways for normal catecholamine metabolism.
- Tolcapone's use is limited by the potential for fatal liver toxicity, requiring strict monitoring of liver function. Reserve tolcapone for patients with fluctuations unresponsive to other therapies.
- Because entacapone has a shorter half-life, 200 mg is given with each dose of carbidopa/levodopa up to eight times a day.
- Dopaminergic adverse effects may occur and are managed by reducing the carbidopa/levodopa dose. Brownish orange urine discoloration may occur (as with tolcapone), but hepatotoxicity is not reported with entacapone.

Dopamine Agonists

- The ergot derivative **bromocriptine** and the nonergots **pramipexole**, **rotigotine**, and **ropinirole** are beneficial adjuncts in patients experiencing fluctuation in response to levodopa. They decrease the frequency of "off" periods and provide an levodopa-sparing effect.
- Titrate the dose of dopamine agonists slowly to enhance tolerability, and find the least dose that provides optimal benefit (see **Table 57-2**).
- The nonergots are safer and are effective as monotherapy in mild-to-moderate PD and as adjuncts to levodopa in patients with motor fluctuations.
- There is less risk of developing motor complications from monotherapy with dopamine agonists than from levodopa. Because younger patients are more likely to develop motor fluctuations, dopamine agonists are preferred in this population. Older patients are more likely to experience psychosis and orthostatic hypotension from dopamine agonists; therefore, carbidopa/levodopa may be the best initial medication in elderly patients. For patients with cognitive problems or dementia, dopamine agonists are best avoided.
- Common side effects of dopamine agonists are shown in **Table 57-3**. Other side effects include vivid dreams and sleep attacks. When added to levodopa, dopamine agonists may worsen dyskinesias. Hallucinations or delusions should be managed by dosage reduction or discontinuation and if needed addition of an atypical antipsychotic, such as clozapine, quetiapine, or pimavanserin (FDA approved for psychosis in PD).
- **Bromocriptine** is not commonly used because of its safety profile, which includes a risk of pulmonary fibrosis.
- **Pramipexole** is primarily renally excreted, and the initial dose must be adjusted in renal insufficiency. A once-daily extended-release formulation is available.
- **Ropinirole** is metabolized by cytochrome P4501A2; fluoroquinolones and smoking may alter ropinirole clearance. A once-daily formulation is available.
- **Rotigotine** patch provides continuous release over 24 hours, and disposition is not affected by hepatic or renal impairment.
- **Apomorphine** is a nonergot dopamine agonist given as a subcutaneous "rescue" injection. For patients with advanced PD with intermittent "off" episodes despite optimized therapy, subcutaneous apomorphine triggers an "on" response within 20 minutes, and duration of effect is up to 100 minutes. Most patients require 0.06 mg/kg. Prior to injection, patients should be premedicated with the antiemetic **trimethobenzamide**. It is contraindicated with the serotonin-3-receptor blockers (eg, ondansetron).

EVALUATION OF THERAPEUTIC OUTCOMES

- Comprehensive monitoring is essential to achieve desired outcomes (**Table 57-5**). Educate patients and caregivers about recording medication doses and administration times and duration of "on" and "off" periods.

- Monitor symptoms, side effects, and activities of daily living, and individualize therapy. Concomitant medications that may worsen motor symptoms, memory, falls, or behavioral symptoms should be discontinued if possible.

TABLE 57-5

Monitoring Parkinson Disease Therapy

1. Monitor medication administration times. Educate the patient that immediate-release carbidopa/levodopa 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 levodopa 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 drugs that can exacerbate idiopathic Parkinson disease motor features (eg, D_2-receptor blockers).
7. Monitor for presence of drugs that can exacerbate nonmotor symptoms. Evaluate whether the presence of an anticholinergic agent is causing confusion or cognitive impairment.

See Chapter 76, Parkinson Disease, authored by Jack J. Chen and Khashayar Dashtipour, for a more detailed discussion of this topic.