Parkinson Disease (PD) is a chronic, progressive movement disorder resulting from loss of dopamine from the nigrostriatal tracts in the brain, and is characterized by rigidity, bradykinesia, postural disturbances, and tremor.

Treatment for PD is aimed at restoring dopamine supply through one, or a combination, of the following methods: exogenous dopamine in the form of a precursor, levodopa; direct stimulation of dopamine receptors via dopamine agonists; and inhibition of metabolic pathways responsible for degradation of levodopa.

Therapy for PD is usually delayed until there is a significant effect on quality of life; generally younger patients start with dopamine agonists, whereas older patients may start with levodopa.

Initial therapy with dopamine agonists is associated with a lower risk of developing motor complications than with levodopa, but all patients will eventually require levodopa.

Advanced PD is characterized by motor fluctuations including a gradual decline in on time, and the development of troubling dopaminergic-induced dyskinesias. Dopamine agonists, monoamine oxidase type B (MAO-B) inhibitors, and catechol-O-methyltransferase (COMT) inhibitors can reduce motor fluctuations; amantadine can improve dyskinesias. Deep brain stimulation of the globus pallidus interna or subthalamic nucleus may benefit patients with advanced PD.

It is controversial whether any therapies for PD are truly disease-modifying or neuroprotective.

Comprehensive therapy for patients should include attention to the many progressive complications of PD, including neuropsychiatric disturbances and autonomic dysfunction.

Dopamine agonists are first-line treatments for restless leg syndrome (RLS). They are preferred because they are longer acting than levodopa, and reduce symptoms throughout the entire night. Other effective therapies include carbidopa/levodopa, gabapentin, benzodiazepines, and opiates.

A common problem with long-term use of dopaminergic agents in RLS, particularly levodopa, is an augmentation effect. This refers to a gradual dosage intensification that occurs in response to a progressive worsening of symptoms after an initial period of improvement. Gradual withdrawal of therapy and substitution with other agents should be performed, rather than continued dopaminergic dose escalation.
ESSENTIAL TREMOR

1. Essential tremor should be distinguished clinically from tremor associated with PD or other causes.

Treatments of choice for essential tremor include propranolol or primidone. In refractory cases, targeted botulinum toxin A injections can be useful.

PARKINSON DISEASE

Incidence, Prevalence, and Epidemiology

Parkinson disease (PD) is a chronic, progressive movement disorder in which drug therapy plays a central role. Since its original description in 1817 by Dr. James Parkinson, the term parkinsonism has come to refer to any disorder associated with two or more features of tremor, rigidity, bradykinesia, or postural instability. Most cases of PD are of unknown cause, and referred to as idiopathic parkinsonism; however, viral encephalitis, cerebrovascular disease, and hydrocephalus have symptoms similar to PD as part of their clinical presentation. Unless otherwise stated, all references to PD in this chapter refer to the idiopathic type.

The age at onset of PD is variable, usually between 50 and 80 years, with a mean onset of 55 years. Both the incidence and prevalence of PD are age-dependent, with annual incidence estimates ranging from 10 cases per 100,000 (age 50–59 years) to 100 cases per 100,000 (age 80–89 years), and an estimated prevalence of 1% of the population older than 65 years of age. Men are affected slightly more frequently than women. Despite the availability of effective symptomatic treatments to improve both quality of life and life expectancy, no cure exists. The symptoms of PD itself do not cause death; however, patients often succumb to complications related to impaired mobility and function (e.g., aspiration pneumonia, thromboembolism) and overall frailty.

Etiology

The etiology of PD is poorly understood. Most evidence suggests it is multifactorial, and attributable to a complex interplay between age-related changes in the nigrostriatal tract, underlying genetic risks, and environmental triggers. Support for this hypothesis can be found in several historic observations, most notably the postural parkinsonian symptoms occurring after epidemics of encephalitis in the early 1900s, and the discovery that ingestion of a meperidine analog, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), by heroin addicts in northern California during the early 1980s caused a rapid and irreversible parkinsonism. (For an excellent in-depth discussion of the importance of the MPTP discovery and its influence on PD research, please view the episode “My Father, My Brother, and Me,” from the Public Broadcasting System program Frontline at http://www.pbs.org/wgbh/pages/frontline/parkinsons/).

The relative contributions of environment and genetics to the occurrence of PD remains controversial; rural living, pesticide exposure, and consumption of well water have consistently been associated with increased lifetime risk of PD, whereas cigarette smoking and caffeine ingestion appear protective. Mutations in several genes, including α-synuclein (SNCA), leucine-rich repeat kinase 2 (LRRK2), parkin, PTFEN-induced kinase-1 (PINK1), and DJ-1, have been observed in rare familial inherited cases of PD, but these genes lack typical Mendelian patterns of inheritance, and do not account for the threefold increased risk of developing PD for individuals who have a first-degree relative affected with sporadic PD. Recent advances in molecular genetics and genome-wide association studies have revealed other novel risk genes; however, the exact linkage between genetics, environment, and clinical expression of disease remains uncertain.

Pathophysiology

PD affects the portion of the extrapyramidal system of the brain involving the basal ganglia, an area composed of the substantia nigra, neostriatum, and globus pallidus. Together, they are involved with maintaining posture and muscle tone and regulating voluntary smooth motor activity. The pigmented neurons within the substantia nigra have dopaminergic fibers that project into the neostriatum and globus pallidus, and in PD, these dopamine-producing neurons are progressively depigmented.

For an image of the areas of the brain affected by PD, go to http://thepoint.lww.com/AT10e.

Postmortem pathologic examination of the basal ganglia reveals the presence of Lewy bodies within the remaining dopaminergic cells of the substantia nigra. These abnormal intraneuronal protein aggregates are considered pathognomonic for the disease. Lewy body pathology appears to ascend the brain in a predictable manner in PD, beginning in the medulla oblongata in preclinical stages (which may explain observations of anxiety, depression, and olfactory disturbance), ascending to the midbrain (motor dysfunction), and spreading eventually to the cortex (cognitive and behavioral changes). The oxidative stress imparted by these events may provide the stimulus for inflammation and cellular apoptosis, thereby initiating the cascade of neurodegeneration. The finding that a critical threshold of neuronal loss (at least 70%–80%) occurs before PD becomes...
Overview of Drug Therapy

Because the salient pathophysiologic feature of PD is the progressive loss of dopamine from the nigrostriatal tracts in the brain, drug therapy for the disease is aimed primarily at replenishing the supply of dopamine (Table 57-1). This is accomplished through one, or a combination, of the following methods: (a) administering exogenous dopamine in the form of a precursor, levodopa, (b) stimulating dopamine receptors within the corpus striatum through the use of dopamine agonists (e.g., pramipexole, ropinirole), or (c) inhibiting the major metabolic pathways within the brain that are responsible for the degradation of levodopa and its metabolites. This latter effect is achieved through the use of aromatic L-amino acid decarboxylase (AADC) inhibitors (e.g., carbidopa), catechol-O-methyltransferase (COMT) inhibitors (e.g., entacapone), or monooamine oxidase type B (MAO-B) inhibitors (e.g., selegiline, rasagiline). Additional therapies such as anticholinergics may be used to improve tremor thought to be attributable to the relative increase in cholinergic activity that occurs as a consequence of loss of dopamine mediated inhibition of acetylcholine neurons. Their routine use, however, is limited by central nervous system adverse effects, particularly in older patients. Amantadine is also used occasionally, and may provide modest benefits via both dopaminergic and nondopaminergic (inhibition of glutamate) mechanisms.

Despite optimization of both pharmacologic and nonpharmacologic therapies in PD, physical disability is progressive and unavoidable. In many instances, adverse effects of the medications themselves can lead to additional problems. Supportive drug treatment of the associated comorbidities of PD is also necessary. These include neuropsychiatric problems (cognitive impairment and dementia, hallucinations and delirium, depression, agitation, anxiety), autonomic dysfunction (constipation, urinary problems, sexual problems, orthostasis, thermoregulatory imbalances), falls, and sleep disorders (insomnia or sleep fragmentation, nightmares, restless leg syndrome).

CLINICAL PRESENTATION OF PARKINSON DISEASE

CASE 57.1

QUESTION 1: L.M., a 55-year-old, right-handed male artist, presents to the neurology clinic complaining of difficulty painting because of unsteadiness in his right hand. On questioning, he notes that it is becoming increasingly difficult to get out of chairs after sitting for a long period because of tightness in his arms and legs. He also reports having a loss in sense of smell and has noticed excessive drooling, especially at night. His wife claims that he has become more “forgetful” lately, and L.M. admits that his memory does not seem to be as sharp as it once was. His medical history is significant for depression for the past year, gout (currently requiring no treatment), constipation, benign prostatic hypertrophy, and aortic stenosis. He does not smoke, but usually drinks one alcoholic beverage in the evenings. His only prescription medication is cilazapram 10 mg/day. On physical examination, L.M. is noted to be a well-developed, well-nourished man who displays a notable lack of normal changes in facial expression and speaks in a soft, monotone voice. A strong body odor is noted. Examination of his extremities reveals a slight ratchetlike rigidity in both arms and legs, and a mild resting tremor is present in his right hand. His gait is slow but otherwise normal, with a slightly bent posture. His balance is determined to be normal, with no retropropulsion or loss of righting reflexes after physical threat. His genitourinary examination is remarkable only for prostatic enlargement. The remainder of L.M.’s physical examination is within normal limits. Laboratory values and vital signs obtained at this visit include the following:

- Blood pressure, 119/66 mm Hg
- Heart rate, 71 beats/minute
- Sodium, 132 mEq/L
- Potassium, 4.4 mEq/L
- Blood urea nitrogen, 19 mg/dL
- Creatinine, 1.1 mg/dL
- Thyroid stimulating hormone, 3.65 microunits/L
- Vitamin B₁₂, 612 pg/mL
- Folate, 5.2 ng/mL
- White blood cells, 4,400 cells/μL
- Red blood cells, 5.9 × 10¹²/μL
- Hemoglobin, 13.8 g/dL
- Hematocrit, 41%
- Uric acid, 6.3 mg/dL

How is PD diagnosed? What signs and symptoms suggestive of PD are present in L.M.? Which of these symptoms are among the classic symptoms for diagnosing PD, and which are considered associated symptoms? Is neuroimaging or any other testing helpful in establishing the diagnosis of PD?

The foundation for establishing the diagnosis of PD remains firmly grounded in obtaining a careful history and physical examination. The neurologic examination to assess motor function, along with a positive response to levodopa, is highly diagnostic. The search for biomarkers of premotor PD in blood, cerebrospinal fluid, and urine has not uncovered any useful candidates. Likewise, although positron emission tomography and single photon emission computed tomography imaging can visualize nigrostriatal nerve terminals of dopamine synthesis and identify presymptomatic pathology, their use remains investigational and largely confined to enriched populations of asymptomatic first-degree relatives of patients with PD. Although these methods are highly sensitive and specific, the application of such imaging techniques into routine practice in asymptomatic at-risk individuals is not yet justified. Other associated premotor symptoms, such as hyposmia (a reduced ability to smell and detect odors) and rapid eye movement sleep disorder, are among the earliest symptoms to appear; screening for these findings may prove more economically practical and identify a population at higher risk and worthy of further study. An example of such a strategy can be found in the longitudinal Parkinson Associated Risk Study (http://www.parsinfosource.com), which uses an inexpensive but sensitive screening test of olfactory disturbances to select asymptomatic individuals at risk for PD to undergo further neuroimaging. Those with pathology identified from neuroimaging are then observed longitudinally for the development of motor symptoms. By the time patients present with symptoms such as L.M., a substantial burden of neuropathologic evidence has accumulated, and the diagnosis can be made clinically. Therefore, further laboratory or radiological testing is unnecessary.
<table>
<thead>
<tr>
<th>Medications Used for the Treatment of Parkinson Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Generic (Trade) Name</strong></td>
</tr>
<tr>
<td>Amantadine (Symmetrel)</td>
</tr>
<tr>
<td>Anticholinergic Agents</td>
</tr>
<tr>
<td>Benztropine (Cogentin)</td>
</tr>
<tr>
<td>Trihexyphenidyl (Artane)</td>
</tr>
<tr>
<td>Combination Agents</td>
</tr>
<tr>
<td>Carbidopa-Levodopa (immediate-release)/entacapone (Stalevo)</td>
</tr>
<tr>
<td>Dopamine Agonists</td>
</tr>
<tr>
<td>Bromocriptine (Parlodel)</td>
</tr>
<tr>
<td>Pramipexole (Mirapex, Mirapex ER)</td>
</tr>
<tr>
<td>Rotigotine (Neupro)</td>
</tr>
</tbody>
</table>

(continued)
TABLE 57-1
Medications Used for the Treatment of Parkinson Disease (Continued)

<table>
<thead>
<tr>
<th>Generic (Trade) Name</th>
<th>Dosage Unit</th>
<th>Titration Schedule</th>
<th>Usual Daily Dose</th>
<th>Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>COMT Inhibitors</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Entacapone (Comtan)</td>
<td>200-mg tablet</td>
<td>One tablet with each administration of levodopa/carbidopa, up to 8 tablets daily</td>
<td>3–8 tablets daily</td>
<td>Diarrhea, dyskinesias, abdominal pain, urine discoloration</td>
</tr>
<tr>
<td>Tolcapone (Tasmar)</td>
<td>100–200 mg tablet</td>
<td>100–200 mg TID</td>
<td>300–600 mg divided TID</td>
<td>Diarrhea, dyskinesias, abdominal pain, urine discoloration, hepatotoxicity</td>
</tr>
</tbody>
</table>

**MAO-B Inhibitors**

<table>
<thead>
<tr>
<th>Generic (Trade) Name</th>
<th>Dosage Unit</th>
<th>Titration Schedule</th>
<th>Usual Daily Dose</th>
<th>Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Selegiline (Eldepryl)</td>
<td>5-mg tablet, capsule</td>
<td>5 mg, may increase to 5 mg BID</td>
<td>5-10 mg /take 5 mg with breakfast and 5 mg with lunch)</td>
<td>Insomnia, dizziness, nausea, vomiting, asthenia, dyskinesias, mood changes; use caution when coadministered with sympathomimetics or serotoninergic agents (increased risk of serotonin syndrome); avoid tyramine-containing foods</td>
</tr>
<tr>
<td>Selegiline ODT (Zelapar)</td>
<td>1.25-mg tablet</td>
<td>1.25 mg every day; may increase to 2.5 mg every day after 6 weeks</td>
<td>1.25–2.5 mg every day</td>
<td>Insomnia, dizziness, nausea, vomiting, asthenia, dyskinesias, mood changes; use caution when coadministered with sympathomimetics or serotoninergic agents (increased risk of serotonin syndrome); avoid ingestion large amounts of tyramine-containing foods</td>
</tr>
<tr>
<td>Rasagiline (Azilect)</td>
<td>0.5-mg tablet</td>
<td>0.5 mg every day; may increase to 1 mg every day</td>
<td>0.5–1 mg/day</td>
<td>Similar to selegiline</td>
</tr>
</tbody>
</table>

*Not currently available in the United States.*

*Transdermal formulation is also available, but not approved for use in PD.

**BID,** twice daily; **COMT,** catechol-O-methyltransferase; **HS,** bedtime; **MAO-B,** monoamine oxidase type B; **ODT,** orally disintegrating tablet; **QID,** four times daily; **TID,** three times daily.

The classic features of PD—tremor, limb rigidity, and bradykinesia—are easily recognized, particularly in advanced stages of disease. However, it is important to note that not all are required to be present to make the diagnosis of PD. The presence of two or more features indicates clinically probable PD.15 Tremor, which is most often the first symptom observed in younger patients, is usually unilateral on initial presentation. Frequently, the tremor is of a pill rolling type involving the thumb and index finger (3–6 Hz); it is present at rest, worsens under fatigue or stress, and is absent with purposeful movement or when asleep.1 These features help distinguish it from essential tremor, which usually manifests as a symmetric tremor in the hands, often accompanied by head and voice tremor.12 Approximately 30% of patients with idiopathic PD do not present with tremor.15 Muscular rigidity resulting from increased muscle tone often manifests as a cogwheel or ratchet (catch-release) type of motion when an extremity is moved passively.1 Rigidity may also be experienced as stiffness or vague aching or limb discomfort.16 Bradykinesia refers to an overall slowness in initiating movement. Early in the disease, patients may describe this as weakness or clumsiness of a hand or leg.17 As the disease progresses, difficulty initiating and terminating steps results in a hurried or festinating gait; the posture becomes stooped (simian posture), and postural reflexes are impaired.1 Patients with PD develop masked facies, or a blank stare with reduced eye blinking (Fig. 57-1).
L.M. has benign prostatic hypertrophy and may benefit from further evaluation. He should be counseled to avoid anticholinergic agents that may exacerbate this problem. He should be referred to a speech and swallowing expert because dysphagia can result in impaired swallowing and lead to aspiration; a soft diet may be indicated. The soft, mumbled, monotone voice noted in L.M. is frequently observed in PD and often one of the early symptoms noted. Speech therapy can be of benefit.11 Psychiatric disturbances, such as nervousness, anxiety, and depression, occur commonly in patients with PD, and regular screening for these symptoms should occur.12-14 L.M. has a history of depression treated with citalopram that could be attributable to PD, and his therapy should be periodically evaluated. Finally, the prevalence of cognitive decline and dementia among patients with PD ranges from 10% to 30% and may be associated with a more rapid progression of disease-related disability.1 The development of hallucinations in patients with PD with dementia is a poor prognostic sign. The forgetfulness and decreased memory described by L.M. could be early signs of cognitive decline and warrant close observation.

Staging of Parkinson Disease

CASE 57-1. QUESTION 2. What are the stages of PD? In what stage of the disease is L.M.? To assess the degree of disability and determine the rate of disease progression relative to treatment, various scales have been developed. The most common of these is the Hoehn and Yahr scale (Table 57-2).1-7 In general, patients in Hoehn and Yahr stage 1 or 2 of PD have mild disease that does not interfere with activities of daily living or work and usually requires minimal or no treatment. In stage 3 disease, daily activities are restricted and employment may be significantly affected unless effective treatment is initiated. L.M. appears to be in late stage 2, early stage 3 of the disease according to the scale.

TABLE 57-2 Staging of Disability in Parkinson Disease

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Unilateral involvement only; minimal or no functional impairment</td>
</tr>
<tr>
<td>2</td>
<td>Bilateral involvement, without impairment of balance</td>
</tr>
<tr>
<td>3</td>
<td>Evidence of postural imbalance; some restriction in activities; capable of leading independent life; mild to moderate disability</td>
</tr>
<tr>
<td>4</td>
<td>Severely disabled, cannot walk and stand unassisted; significantly incapacitated</td>
</tr>
<tr>
<td>5</td>
<td>Restricted to bed or wheelchair unless aided</td>
</tr>
</tbody>
</table>

Because L.M. is an artist, this abnormality would be particularly troublesome. He also is showing signs of autonomic nervous system dysfunction, such as drooling (sialorrhea), seborrhea, and constipation, all of which can be particularly embarrassing to the patient. Drooling may be a consequence of impaired swallowing. The strong body odor exhibited by L.M. could be ascribed to excess sebum production. L.M.’s seborrhea can be treated with coal tar- or selenium-based shampoos, or topical ketoconazole. His constipation should be managed first by evaluating his diet and exercise level, discontinuing anticholinergic medications (including over-the-counter cold and sleep medications) that may exacerbate constipation, and using a stool softener such as sodium or calcium docusate. In more severe cases, polyethylene glycol, lactulose, milk of magnesia, or enemas may be required.

L.M. should be evaluated for other manifestations of autonomic dysfunction, including urinary problems, increased sweating, orthostatic hypotension, erectile dysfunction, pain or dysesthesias, and problems swallowing.

For a video that shows the postural control challenges posed by Parkinson disease, go to http://thepoint.lww.com/AT11e.
With advanced-stage disease (3 to 4), most patients require levodopa therapy (with a peripheral decarboxylase inhibitor such as carbidopa) and often in combination with a COMT inhibitor such as entacapone or a dopamine agonist such as pramipexole or ropinirole. In some cases, selegiline, rasagiline, or amantadine may provide further symptomatic relief. Patients with end-stage disease (stage 5) are severely incapacitated and, because of advanced disease progression, often do not respond well to drug therapy.

TREATMENT OF PARKINSON DISEASE

CASE 57-1, QUESTION 3: When should L.M. begin treatment for his PD?

In choosing when to treat the symptoms of PD and which therapy to use, care must be taken to approach each patient individually. Although no consensus has been reached about when to initiate symptomatic treatment, most healthcare professionals agree that treatment should begin when the patient begins to experience functional impairment as defined by (a) threat to employment status, (b) symptoms affecting the dominant side of the body, or (c) bradykinesia or rigidity. Individual patient preferences also should be considered. Judging by the symptoms L.M. is displaying, he would likely benefit from immediate treatment. His symptoms are unilateral but are occurring on his dominant side and are interfering with his ability to paint, thus affecting his livelihood. He is also showing signs of rigidity and bradykinesia but can otherwise live independently.

An algorithm for the management of patients with PD is presented in Figure 57-2. The long-term, individualized treatment...
8

plan is usually characterized by frequent dosage adjustments with time because of the chronic and progressive nature of the disease. Although most of this chapter is devoted to the drug therapy of PD, the importance of supportive care cannot be overemphasized. Exercise, physiotherapy, and good nutritional support can be beneficial at the earlier stages to improve mobility, increase strength, and enhance well-being and mood. Psychological support is often necessary in dealing with depression and other related problems. Newly diagnosed patients and their family members need to be educated about what to expect from the disease and the various forms of treatment available. The support of family members is vital in establishing an overall effective therapeutic plan.

**Dopamine Agonists**

**INITIAL THERAPY**

**CASE 57-1, QUESTION 4: The decision is made to begin drug therapy for L.M. Should therapy be initiated with a dopamine agonist or levodopa?**

Levodopa remains the most effective antiparkinsonian agent. However, monotherapy with levodopa throughout the entire course of the disease is limited by response fluctuations and declining efficacy as PD progresses. Escalating doses of levodopa are accompanied by a high frequency of undesirable side effects; thus, other methods of enriching dopamine supply have been developed. Dopamine agonists, which directly bind to dopamine receptors, are one such group of agents. In clinical trials comparing dopamine agonists with levodopa, activities of daily living (ADLs) and motor features are improved 40% to 50% with levodopa compared with 10% with dopamine agonists. Although they are not as effective as levodopa, the dopamine agonists have a number of potential advantages. Because they act directly on dopamine receptors, they do not require metabolic conversion to an active product and therefore act independently of degenerating dopaminergic neurons. Unlike levodopa, circulating plasma amino acids do not compete with dopamine agonists for absorption and transport into the brain. Dopamine agonists have a longer half-life than levodopa formulations, reducing the need for multiple daily dosing. Initial therapy with dopamine agonists is associated with fewer motor complications such as dyskinesias, and can delay the need for initiation of dopamineergic therapy. As a class, dopamine agonists provide adequate control of symptoms when given as monotherapy in up to 80% of patients with early-stage disease. These benefits are sustained for 3 years or more in most patients. However, with disease progression, levodopa therapy will eventually be required.

Guidelines from the American Academy of Neurology support either dopamine agonists or levodopa as initial therapy for PD. In younger patients (e.g., age <65 years) with milder disease, such as L.M., the initiation of a dopamine agonist as a first-line agent is a strategy used to delay the introduction of levodopa. Delaying levodopa allows patients to have a longer period of time before experiencing motor complications, particularly troubling peak-dose levodopa-induced dyskinesias, which eventually develop with advancing PD. In older patients (e.g., age >65 years) with PD, it may be more appropriate to initiate treatment with levodopa instead of a dopamine agonist because these patients are more likely to experience intolerable central nervous system side effects from dopamine agonists.

In the case of L.M., his relatively young age (<65 years) and mild disease make him a good candidate for initial therapy with a dopamine agonist. L.M. will require levodopa therapy at a later time, when he reaches more advanced stages of the disease. By initiating therapy first with a dopamine agonist, rescue levodopa therapy can likely be started at smaller doses, and the onset of motor complications that often occur with escalating doses and extended therapy with levodopa may be delayed.

**SELECTION OF AGENTS**

**CASE 57-1, QUESTION 5: L.M. is to be started on a dopamine agonist. Which agent should be selected?**

Two generations of dopamine agonists have been used for the treatment of idiopathic, early-stage PD as monotherapy, or as an adjunct to levodopa in patients with advanced disease. The comparative pharmacologic and pharmacokinetic properties of these agents are shown in Table 57-3. The first-generation dopamine agonists, which are derived from ergot alkaloids, include bromocriptine, pergolide, and cabergoline. These older agents are now rarely used because of increased risk of retroperitoneal fibrosis, as well as a twofold to fourfold increased risk for cardiac valve fibrosis, when compared with nonergoline dopamine agonists and controls. Pergolide was voluntarily withdrawn in the United States in 2007 for this reason, and although cabergoline continues to be used in Europe, it is only indicated in the United States for treating hyperprolactinemia. Pramipexole, ropinirole, apomorphine, and rotigotine are second-generation nonergoline dopamine agonists. Of

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**Table 57-3**

**Pharmacologic and Pharmacokinetic Properties of Dopamine Agonists**

<table>
<thead>
<tr>
<th></th>
<th>Bromocriptine</th>
<th>Pramipexole</th>
<th>Ropinirole</th>
<th>Apomorphine</th>
<th>Rotigotine</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Type of compound</strong></td>
<td>Ergot derivative</td>
<td>Nonergoline</td>
<td>Nonergoline</td>
<td>Nonergoline</td>
<td>Nonergoline</td>
</tr>
<tr>
<td><strong>Receptor specificity</strong></td>
<td>D&lt;sub&gt;2&lt;/sub&gt;, D&lt;sub&gt;4&lt;/sub&gt;, α&lt;sub&gt;2&lt;/sub&gt;, 5-HT&lt;sub&gt;2&lt;/sub&gt;</td>
<td>D&lt;sub&gt;2&lt;/sub&gt;, D&lt;sub&gt;4&lt;/sub&gt;, α&lt;sub&gt;2&lt;/sub&gt;, 5-HT&lt;sub&gt;2&lt;/sub&gt;</td>
<td>D&lt;sub&gt;2&lt;/sub&gt;, D&lt;sub&gt;4&lt;/sub&gt;, α&lt;sub&gt;2&lt;/sub&gt;, 5-HT&lt;sub&gt;2&lt;/sub&gt;</td>
<td>D&lt;sub&gt;2&lt;/sub&gt;, D&lt;sub&gt;4&lt;/sub&gt;, α&lt;sub&gt;2&lt;/sub&gt;, 5-HT&lt;sub&gt;2&lt;/sub&gt;</td>
<td>D&lt;sub&gt;2&lt;/sub&gt;, D&lt;sub&gt;4&lt;/sub&gt;, α&lt;sub&gt;2&lt;/sub&gt;, 5-HT&lt;sub&gt;2&lt;/sub&gt;</td>
</tr>
<tr>
<td><strong>Bioavailability</strong></td>
<td>8%</td>
<td>&gt;90%</td>
<td>55% (first pass metabolism)</td>
<td>&lt;1% orally, 100% subcutaneous</td>
<td>10–40</td>
</tr>
<tr>
<td><strong>T&lt;sub&gt;1/2&lt;/sub&gt; (minutes)</strong></td>
<td>70–100</td>
<td>60–100</td>
<td>90</td>
<td>10–40</td>
<td>15–18 (hours); no characteristic peak observed</td>
</tr>
<tr>
<td><strong>Protein binding</strong></td>
<td>98–99%</td>
<td>15%</td>
<td>40%</td>
<td>&gt;95%</td>
<td>&gt;95%</td>
</tr>
<tr>
<td><strong>Elimination route</strong></td>
<td>Hepatic</td>
<td>Renal</td>
<td>Hepatic</td>
<td>Hepatic</td>
<td>Hepatic</td>
</tr>
<tr>
<td><strong>Half-life (hours)</strong></td>
<td>3–8</td>
<td>6–12</td>
<td>6</td>
<td>0.5–1</td>
<td>3</td>
</tr>
</tbody>
</table>

*Not currently available in the United States.

**Antagonist**

5-HT, serotonin.
In a long-term September 17, 2011 2:31
The mean pramipexole main-

6.0 years) has

Similar to pramipexole, ropinirole is

Although the drug

These trials were multicenter,

At the end of 5 years, the mean daily dose

Doses could

Stimu-

Dopamine agonists work by directly stimulating postsynaptic dopamine receptors within the corpus striatum. The two families of dopamine receptors are D1 and D2. The D2 family includes the D2a, D2b, and D2c dopamine subtype receptors and the D3 family includes D3a, D3b, and D3c dopamine subtype receptors. Stimulation of D2 receptors is largely responsible for reducing rigidity and bradykinesia, whereas the precise role of the D1 receptors remains uncertain. Although the dopamine agonists differ slightly from each other in terms of their affinities for dopamine receptor subtypes, these agents produce similar clinical effects when used to treat PD, and no compelling evidence favors one agent over another strictly on efficacy measures. Instead, experience with the nonergoline dopamine agonists, pramipexole or ropinirole, makes them currently preferred as initial dopamine agonists. No studies have directly compared these two agents, and individual studies of efficacy appear to demonstrate similar benefits. Thus, either agent would be acceptable as initial therapy in LM.

CASE 57-1, QUESTION 6: The decision is made to begin pramipexole in LM. How effective is pramipexole in the initial treatment of PD? How does ropinirole compare?

PRAMIPEXOLE
Pramipexole has been well studied as monotherapy in patients with early-stage PD,\textsuperscript{30,31} and as an adjunct to levodopa therapy in advanced-stage disease.\textsuperscript{32,33} These trials were multicenter, placebo-controlled, parallel group studies, and the primary outcome measures included improvement in ADLs (part II) and motor function scores (part III) as measured by the Unified Parkinson Disease Rating Scale (UPDRS). (Go to http://www.mndu.org/library/ratingscales/pd/ to download this document.) Each evaluation on the UPDRS is rated on a scale of 0 (normal) to 4 (can barely perform). Lower scores on the UPDRS after treatment indicate an improvement in overall performance.

The evidence for pramipexole’s efficacy in early PD comes from two large-scale, double-blind, placebo-controlled studies that included a total of 599 patients with early-stage PD (mean disease duration of 2 years).\textsuperscript{34,35} In the first study, 264 patients were randomly assigned to receive one of four fixed doses (1.5, 3.0, 4.5, or 6.0 mg/day) or placebo.\textsuperscript{36} The pramipexole-treated patients had a 20% reduction in their total UPDRS scores compared with baseline values, whereas no significant improvement was observed in the placebo-treated patients. A trend toward decreased tolerability was noted as the pramipexole dosage was escalated, especially in the 6.0-mg/day group. A second study of 333 patients treated doses up to the maximal tolerated dose (not to exceed 4.5 mg/day) and then followed patients for a 6-month maintenance phase.\textsuperscript{37} The mean pramipexole maintenance dosage was 3.8 mg/day. Those treated with pramipexole experienced significant improvements in both the ADL scores (22%–29%) and motor scores (25%–31%), whereas there were no significant changes in the placebo group (p < 0.001).

Against levodopa as initial therapy, pramipexole appears to delay the onset of dyskinesias. In a randomized, controlled trial evaluating the development of motor complications with the two therapies, 301 untreated patients with early PD were randomly assigned to receive either pramipexole 0.5 mg three times daily or carbidopa/levodopa 25/100 mg three times daily.\textsuperscript{38} Doses could be escalated during the first 10 weeks of the study, after which open-label levodopa was permitted if necessary. The primary end point was the time to the first occurrence of wearing off, dyskinesias, or on-off motor fluctuations. After a mean follow-up of 24 months, patients in the pramipexole group were receiving a mean daily dose of 2.78 mg pramipexole and 264 mg of supplemental levodopa, whereas patients in the levodopa group were receiving a mean total of 509 mg/day levodopa. Fewer pramipexole-treated patients reached the primary end point (28% vs. 31%, p < 0.001) than the patients initially randomly assigned to levodopa therapy. Dyskinesias were noted in only 10% of pramipexole-treated patients compared with 31% of levodopa-treated patients (p < 0.01), and fewer patients experienced wearing off effects with pramipexole (24% vs. 38%; p = 0.01). Long-term follow-up of this cohort (mean = 6.0 years) has revealed a persistently lower rate of dopaminergic motor complications in the pramipexole-treated patients compared with those receiving levodopa (50.0% vs. 68.4%, respectively; p = 0.002).\textsuperscript{39}

ROPINIROLE
Ropinirole is a synthetic nongluteline dopamine agonist with selectivity for D2 receptors, as with pramipexole, however, it has no significant affinity for D1 receptors.\textsuperscript{40} Although the drug is pharmacologically similar to pramipexole, it has some distinct pharmacokinetic properties, as shown in Table 57-3. Unlike pramipexole, which is primarily eliminated by renal excretion, ropinirole is metabolized by the cytochrome P-450 (primarily CYP1A2) oxidative pathway and undergoes significant first-pass hepatic metabolism.\textsuperscript{41} Similar to pramipexole, ropinirole is approved for use as monotherapy in early-stage idiopathic PD and as an adjunct to levodopa therapy in patients with advanced-stage disease.

Ropinirole has not been directly compared with pramipexole in a randomized, double-blind trial, but it appears to have comparable efficacy as inferred from indirect comparison. In several randomized, double-blind, multicenter, parallel group studies comparing it with placebo, bromocriptine, or levodopa, 6 months of monotherapy with ropinirole in patients with early PD significantly improves UPDRS motor scores (approximately 20%–30%) compared with baseline values.\textsuperscript{42}–\textsuperscript{44} In a long-term study, patients treated initially with ropinirole were less likely to experience dyskinesias compared with those treated initially with levodopa.\textsuperscript{45} At the end of 5 years, the mean daily dose of ropinirole was 16.5 mg plus 427 mg of open-label levodopa, compared with a mean daily dose of 753 mg of levodopa for the levodopa group. Of patients in the ropinirole group, 66% required open-label levodopa supplementation compared with 36% in the levodopa group. Dyskinesias developed in 20% of the ropinirole-treated patients compared with 45% of the levodopa-treated patients (hazard ratio for remaining free of dyskinesia in the ropinirole group, compared with the levodopa group, 2.82, p < 0.001). For ropinirole-treated patients who were able to remain on monotherapy without open-label levodopa supplementation, only 9% experienced dyskinesia, compared with 36% of those receiving levodopa monotherapy. The lower incidence of dyskinesia in ropinirole-treated patients was shown to persist in long-term open-label follow-up of this study cohort.\textsuperscript{46}

DOSSING

CASE 57-1, QUESTION 7: How are pramipexole and ropinirole dosed?
Pramipexole and ropinirole should always be initiated at a low dosage and gradually titrated to the maximal effective dose, as tol-tolerability. The frequency of adverse events depends on disease severity and tolerability. One fixed-dose study of pramipexole in early PD showed that most patients responded maximally at a dosage of 0.5 mg three times daily. In patients with advanced-stage disease, an average of 3.4 mg/day is usually required to reach the maximal effect of pramipexole.

L.M. has normal renal function and his pramipexole should be started at an initial dosage of 0.125 mg three times daily for 5 to 7 days. At week 2, the dosage should be increased to 0.25 mg three times daily. Thereafter, his dosage may be increased weekly by 0.25 mg/dose (0.75 mg/day) as tolerated and up to the maximal effective dose, not to exceed 1.5 mg three times daily. The titration period usually takes about 4 to 7 weeks, depending on the optimal maintenance dose. Patients with a creatinine clearance of less than 60 mL/minute should be dosed less frequently than those with normal renal function. Patients with a creatinine clearance of 35 to 59 mL/minute should receive a starting dose of 0.125 mg twice daily up to a maximal dose of 1.5 mg twice daily; patients with a creatinine clearance of 15 to 34 mL/minute should receive a starting dose of 0.125 mg daily up to a maximal dose of 1.5 mg daily. Pramipexole has not been studied in patients with renal insufficiency. Pramipexole is not recommended in patients with a creatinine clearance of less than 15 mL/minute or those receiving hemodialysis. A once-daily extended-release formulation of pramipexole is also available; patients can be switched overnight from immediate-release pramipexole at the same daily dose.

Ropinirole should be initiated at a dosage of 0.25 mg three times daily, with gradual titration in weekly increments of 0.25 mg/dose over the course of 4 to 6 weeks. Clinical response to ropinirole is usually observed at a daily dose of 9 to 12 mg given in three divided doses. Doses may be increased to a maximal daily dose of 24 mg/day. Patients wishing to take the drug less frequently can be switched directly to an extended release once-daily formulation, selecting the dose that most closely matches the total daily dose of the immediate-release formulation. No dose adjustments for ropinirole are necessary in patients with renal dysfunction.

ADVERSE EFFECTS

CASE 57-1, QUESTION 8: What are the adverse effects of pramipexole and ropinirole? How can these be managed?

Because pramipexole and ropinirole are both approved for use as monotherapy in early-stage disease and as adjunctive therapy in advanced-stage disease, the adverse events of these agents have been evaluated as a function of disease stage. In studies of patients with early-stage disease, the most common adverse events were nausea (28%–44%), dizziness (25%–40%), somnolence (22%–40%), insomnia (17%), constipation (14%), asthenia (14%), hallucinations (9%), and leg edema (5%). Nausea, with or without vomiting, can be a significant problem, particularly with higher doses. Administering these drugs with food may partially alleviate this problem. With continued use, many patients exhibit tolerance to the gastrointestinal side effects. Central nervous system side effects were the most common reason for discontinuation of these agents. Older patients are particularly more likely to experience hallucinations and other central nervous system adverse effects with dopamine agonists. The incidence of orthostatic hypotension was relatively low (1%–9%) and may in part reflect the exclusion of patients with underlying cardiovascular disease in several of the studies.

In advanced-stage disease, the most common adverse events of dopamine agonists were nausea (25%), orthostatic hypotension (10%–54%), dystonia (27%), somnolence (11%), confusion (30%), and hallucinations (15%–17%).4,44–46 As expected, in patients with advanced-stage disease, the most common reasons for discontinuing these agents are mental disturbances (nightmares, confusion, hallucinations, insomnia) and orthostatic hypotension. Dyskinesias experienced when dopamine agonists are used in combination with levodopa in advanced-stage disease may require lowering the dose of levodopa or, in some cases, the dopamine agonist.

Sudden, excessive daytime somnolence, including while driving, has been reported with dopamine agonists and has resulted in accidents.40,41,42 Affected patients have not always reported warning signs before falling asleep and believed they were alert immediately before the event. Labeling for these drugs includes a warning that patients should be alerted to the possibility of falling asleep while engaged in daily activities. Patients should be advised to refrain from driving or other potentially dangerous activities until they have gained sufficient experience with the dopamine agonist to determine whether it will hinder their mental and motor performance. Caution should be advised when patients are taking other sedating medications or alcohol in combination with pramipexole and ropinirole. If excessive daytime somnolence does occur, patients should be advised to contact their physician.

Dopamine agonist therapy in patients with PD is associated with a 2- to 3.5-fold increased odds of developing an impulse control disorder.43 The frequency appears similar for both pramipexole and ropinirole. In one study, a prevalence of 6.1% was noted for pathologic gambling in patients with PD compared with 0.25% for age- and sex-matched controls.44 These cases may represent variations of a behavioral syndrome termed levodopa-induced dyskinesia.45,46 Other features of the syndrome have been reported, including punding (carrying out repetitive, purposeless motor acts), hypersexuality, walkabout (having the urge to walk great distances during off times, often with no purpose or destination and abnormalities in time perception), compulsive buying, binge eating, drug hoarding, and social independence or isolation.47 The syndrome appears to be more common among younger, male patients with early-onset PD, as well as those having novelty-seeking personality traits, depressive symptoms, and current use of alcohol or tobacco.48–50 Management of impulse control disorders can be challenging, as it often requires modification of dopaminergic therapies, which must be carefully balanced with the accompanying risk of worsening motor function. Underlying depression, if present, should be treated and may improve impulse control. Nonpharmacologic measures (such as limiting access to money or the Internet) may be helpful, in some cases, antipsychotic drugs may be considered, but must also be used carefully to avoid precipitating motor disability.51

Although L.M. is younger than 65 years of age, he is experiencing memory difficulty and may be at increased risk for visual hallucinations and cognitive problems from dopamine agonist therapy. He should be monitored closely for occurrence or exacerbation of these problems. He should also be evaluated for light-headedness before initiation of pramipexole and counseled to report dizziness or unsteadiness. Because this may lead to falls. He should also be reassured that if these effects are caused by pramipexole, they should subside with time and that he should not drive or operate complex machinery until he can assess the drug’s effect on his mental status. L.M. should be counseled about the possibility of excessive, and potentially unpredictable, daytime somnolence as pramipexole is introduced. L.M. does...
not appear to have a problem with excessive alcohol use; how-
ever, he and his family should be educated about his increased
risk for impulse control disorders and advised to report any
new, unusual or uncharacteristic behaviors or increased use of
alcohol.

**ROTIGOTINE**

**CASE 57-1, QUESTION 9:** What type of dopamine agonist
is rotigotine? How is it used?

Rotigotine is a nonergoline dopamine receptor agonist that
was briefly available in the United States for the treatment
of early-stage idiopathic PD. It remains available in Europe.
Rotigotine is formulated in a transdermal patch delivery sys-
tem designed for one-day application. Transdermal delivery
may provide a more continuous stimulation of dopamine recep-
tors than traditional oral formulations, which in theory may
translate into improved efficacy. Rotigotine has demonstrated
efficacy as monotherapy in early-stage PD and as adjunctive
therapy to levodopa in patients with advanced stages of PD.

Adverse events with rotigotine were similar to those observed
with other dopamine agonists (nausea, vomiting, somnolence,
dizziness).

Rotigotine was voluntarily withdrawn from the US market in
2008 because of problems with crystal formation in the patches,
and faces an uncertain future. Although it continues to be avail-
able in Europe, no timeline has been given for its reintroduction
into the United States.

**Levodopa**

**TIMING OF INITIATION OF THERAPY**

**CASE 57-1, QUESTION 10:** L.M. has responded well to
pramipexole 1.0 mg three times daily (TID) for the past
18 months, with an increased ability to paint and carry
to ADLs. During the past few weeks, however, he has noticed
a gradual worsening in his symptoms and once again is hav-
ing difficulty holding a paintbrush. He currently complains
of feeling more “tied up,” he has more difficulty getting out
of a chair, and his posture is slightly more stooped. He also
notes that he feels tired throughout much of the day. He
remains able to carry out most of his ADLs without assis-
tance. Should levodopa be considered for the treatment of
L.M.’s PD at this time?

Dopamine itself does not cross the blood–brain barrier. Lev-
odopa, a dopamine precursor with no known pharmacologic
action of its own, crosses the blood–brain barrier, where it is
converted by aromatic amino acid (dopa) decarboxylase to
dopamine. For patients with advancing PD, levodopa has been
a mainstay of treatment since the 1960s. Nearly all patients will
eventually require treatment with the drug, regardless of their ini-
tial therapy. Although it is the most effective therapy for treating
the rigidity and bradykinesia of PD, as with other dopaminergic
agents, levodopa does not effectively improve postural instabil-
ity, or reduce dementia, autonomic dysfunction, or freezing, an
type of akinesia that often occurs in advanced-stage dis-
est.

The question of when to begin levodopa in the treatment
of PD has been historically debated. With long-term use, the
efficacy of levodopa decreases (as measured by the total on
time), and the development of motor fluctuations and dyski-
nesias occurs. These observations led to the belief that chronic
levodopa therapy may actually accelerate the neurodegenera-
tive process through formation of free radicals generated by
dopamine metabolism. The Earlier versus Later Levodopa
Therapy in Parkinson’s Disease (ELLDOPA) study was designed
to determine whether long-term use of levodopa accelerates neu-
rodegeneration and paradoxically worsens PD. The investiga-
tors of this study randomly assigned 361 patients with early PD
to either carbidopa/levodopa 37.5/150 mg/day, 75/300 mg/day, or
150/600 mg/day or placebo for 48 weeks followed by a 2-week
withdrawal of treatment. After 42 weeks, the severity of symp-
toms as measured by changes in the total UPDRS decreased more
in the placebo group than in all of the groups receiving levodopa.

The findings of this study provide assurance that levodopa use
does not result in accelerated progression of the disease based
on clinical evaluations.

The optimal time to initiate levodopa therapy must be indi-
vidualized. In untreated individuals, there is little reason to start
levodopa until the patient reports worsening of function (socially,
vocationally, or otherwise). As discussed previously, the need for
levodopa therapy may be delayed by initiating therapy first with a
dopamine agonist. This approach is a particular advantage in
younger patients who will likely live many years with PD. In the
case of L.M., he is now experiencing bothersome symptoms
despite near-maximal dopamine agonist therapy, and it has pro-
gressed sufficiently to threaten his job performance. Although
the dose of pramipexole could be increased, he may experience
more daytime somnolence; thus, levodopa should be added to
his regimen.

**LEVODOPA: ADVANTAGES AND DISADVANTAGES**

**CASE 57-1, QUESTION 11:** What are the advantages and
disadvantages of carbidopa/levodopa versus levodopa alone?

Although levodopa is the most effective agent for PD, it is
associated with many undesirable side effects, such as nausea,
vomiting, and anorexia (50% of patients); postural hypotension
(30% of patients); and cardiac arrhythmias (10% of patients). In
addition, mental disturbances (see Case 57-1, Question 13) are
encountered in 15% of patients, and abnormal involuntary move-
ments (dyskinesias) can be seen in up to 53% of patients during
the first 6 months of levodopa treatment. Because significant
amounts of levodopa are peripherally (extracerebrally) metabo-
lized to dopamine by the enzyme aromatic amino acid (dopa)
decarboxylase, extremely high doses are necessary if adminis-
tered alone. For this reason, levodopa is always coadministered
with a dopa decarboxylase inhibitor.

By combining levodopa with a dopa decarboxylase inhibitor
that does not penetrate the blood–brain barrier, a decrease
in the peripheral conversion of levodopa to dopamine can be
achieved, while the desired conversion within the basal ganglia
remains unaffected (Fig. 57.3). The two peripheral decarboxy-
lase inhibitors in clinical use are benserazide (unavailable in the
United States) and carbidopa. A fixed combination of carbidopa
and levodopa is available in ratios of 2:1 (carbidopa/levodopa
25/100) and 1:1 (carbidopa/levodopa 10/100 and 25/250). A
controlled-release product is available in a ratio of 25/100 and
50/200. In addition, carbidopa/levodopa is also available as an
orally disintegrating tablet.

Combining carbidopa with levodopa enhances the amount
of dopamine available to the brain and thereby allows the dose
of levodopa to be decreased by 80%. This combination also
shortens the time needed to achieve optimal effects by several
weeks, because carbidopa substantially decreases the often dose-
limiting levodopa-induced nausea and vomiting.
Section 13
Neurologic Disorders

Levodopa Levodopa + Decarboxylase Inhibitor

Brain Heart Kidneys Liver Stomach
Levodopa Dopamine Levodopa Dopamine

FIGURE 57-3 Peripheral decarboxylation of levodopa when given alone (left) and with a peripheral decarboxylase inhibitor (right). When combined with a decarboxylase inhibitor, less drug is required and more levodopa reaches the brain. Reproduced with permission from Finder RM et al. Levodopa and decarboxylase inhibitors: a review of their clinical pharmacology and use in the treatment of parkinsonism. Drugs. 1976;11:329.

CARBIDOPA/LEVODOPA DOSING

CASE 57-1, QUESTION 12: The decision is made to begin L.M. on carbidopa/levodopa. How should it be dosed?

About 75 to 100 mg/day of carbidopa is necessary to saturate peripheral dopa decarboxylase. It is usually unnecessary and more costly to give higher amounts of carbidopa than this. Therapy should be initiated with immediate-release carbidopa/levodopa 25/100 at a dose of one tablet three times a day. The immediate-release formulation is preferred because it allows for much easier adjustment of the levodopa dose. In L.M.’s case, the dose can then be increased by 100 mg of levodopa every day or every other day up to eight tablets (800 mg) or to the maximal effective dose, to individual requirements, or as tolerated.

If troublesome peak-dose dyskinesias occur, the following strategies should be considered: the levodopa dose can be lowered but given more frequently; consideration can be given to switching patients to immediate-release if taking controlled-release carbidopa/levodopa (for ease in refining dose adjustments); agents that prolong the half-life of levodopa but do not provide stable levodopa plasma concentrations (e.g., COMT inhibitor, MAO-B inhibitor) can be added; or an antidysonaptic agent such as amantadine can be used. The goal of optimizing therapy lies in balancing the most useful dose (i.e., maximizing the patient’s on time) with that which does not produce unacceptable side effects (i.e., troublesome dyskinesias). Because L.M. is currently being treated with a dopamine agonist, he must be monitored closely for the development of motor complications with the addition of levodopa.

Most patients respond to levodopa doses of 750 to 1,000 mg/day when given with carbidopa. When levodopa doses exceed 750 mg/day, patients such as L.M. can be switched from the 1:4 ratio of carbidopa/levodopa to the 1:10 ratio to prevent providing excessive amounts of decarboxylase inhibitor. For example, if L.M. needed 800 mg/day of levodopa, two carbidopa/levodopa 10/100 tablets four times daily could be given. If L.M. had not been initially treated with a dopamine agonist, some clinicians would consider adding a dopamine agonist after the daily levodopa dose has been increased to more than 600 mg because dopamine agonists directly stimulate dopamine receptors, have longer half-lives, and result in a lower incidence of dyskinesias, thus providing a smoother dopaminergic response. L.M.’s clinical response to levodopa therapy may be improved by modifying dietary amino acid ingestion. Levodopa is actively transported across the blood–brain barrier by a large neutral amino acid transport system. This transport system also facilitates the blood-to-brain transport of amino acids such as l-leucine, l-isoleucine, l-valine, and l-phenylalanine. Levodopa and these neutral amino acids compete for transport mechanisms, and high plasma concentrations of these amino acids can decrease brain concentrations of levodopa. Patients should be instructed to take immediate-release carbidopa/levodopa 30 minutes before or 60 minutes after meals for optimal efficacy.

ADVERSE EFFECTS: MENTAL CHANGES

CASE 57-1, QUESTION 13: Since initiating carbidopa/levodopa, L.M. reports he feels confused at times and has
Although more commonly encountered with dopamine agonists, psychiatric side effects are also associated with levodopa therapy, and include confusion, depression, restlessness and over-activity, psychosis, hypomania, and vivid dreams. Those with underlying or pre-existing psychiatric disorders and those receiving high doses of levodopa for prolonged periods are at greatest risk. Concurrent anticholinergics or amantadine therapy can exacerbate these symptoms. Development of the PD itself correlates with cognitive decline and greater frequency of central nervous system findings, likely mediated through the underlying Lewy body pathology. In some situations it may be difficult to separate the respective drug versus disease effects.

Some patients receiving levodopa experience psychomotor excitation. Symptoms associated with psychomotor activation include overactivity, restlessness, and agitation. Similarly, hypomania has been reported in up to 8% of patients and is characterized by grandiose thinking, flight of ideas, tangential thinking, and poor social judgment. Normal sexual activity often is restored with improved motor function, however, hypersexuality and libido are increased in about 1% of levodopa-treated patients. In general, most of the mental disturbances are dose-related and can be lessened by reducing the dose of the dopaminergic agent. In patients such as L.M. who are concurrently receiving levodopa and a dopamine agonist, the dose reduction should be attempted first with the dopamine agonist. If symptoms do not improve, a reduction in the dose of the levodopa may also be warranted. These dose reductions may, however, be impractical for L.M. because a return of parkinsonian symptoms is likely, and the benefits of levodopa therapy may outweigh the risk for mental disturbances.

Motor Complications

CASE 57-1, QUESTION 14: L.M. had a dramatic improvement in all of his parkinsonian symptoms with the initiation of levodopa therapy after being maintained on 25/250 regular carbidopa/levodopa four times a day. After 6 months of treatment, he began to experience dyskinesias. These usually occurred 1 to 2 hours after a dose and were manifested by facial grimacing, lip smacking, tongue protrusion, and rocking of the trunk. These dyskinetic effects were lessened by decreasing his pramipexole dose to 0.5 mg TID and gradually decreasing his dosage of carbidopa/levodopa to 25/250 TID.

After 3 years of levodopa therapy, more serious problems have begun to emerge. In the mornings, L.M. often experiences immobility. Nearly every day, he has periods (lasting for a few minutes) in which he cannot move, followed by a sudden switch to a fluidlike state, often associated with dyskinetic activity. He continues to take carbidopa/levodopa (25/250 TID), but gains symptomatic relief only for about 3 to 4 hours after a dose. Also, the response to a given dose varies and is often less in the afternoon. At times, he becomes “frozen,” particularly when he needs to board an elevator or is required to move quickly.

For most patients, the initial response to levodopa is favorable, and this early phase is called the honeymoon period. Although variable in each patient, the honeymoon period can last for up to 5 years. After this initial period of stability, 50% to 90% of patients with PD receiving levodopa for 5 or more years will eventually experience motor complications. In evaluating response fluctuations, it is important to ascertain which effects are attributable to the disease and which are attributable to the drug. Levodopa-induced dyskinesias often appear concurrently with the development of motor fluctuations. Peak-dose choreiform dyskinesias are the most common form of dyskinesias that occur with chronic levodopa (and sometimes dopamine agonist) therapy and they frequently subside at the end of the dosing interval. Their severity is related to levodopa dose, disease duration and stage, and younger age at onset. Reducing the levodopa dosage will often reverse these symptoms. However, the reduction in levodopa dosage usually results in deterioration in the control of the disease.

Because levodopa is a short-acting agent with an elimination half-life of about 1.5 hours, much of the effect from the evening dose has dissipated by morning. For this reason, it is not surprising that L.M. is experiencing a period of immobility on arising. This is alleviated in most patients shortly after taking the morning dose.

Two of the more common motor complications are the on-off effect and the wearing off, or end-of-dose deterioration effect. The on-off effect is described as random fluctuations from mobility (often associated with dyskinesias) to the parkinsonian state, which appear suddenly as if a switch has been turned on or off. These fluctuations can last from minutes to hours and increase in frequency and intensity with time. Although most patients prefer to be on despite accompanying dyskinesias, rather than in an off or akineti state, dyskinesias in some patients can be more disabling than the parkinsonism. Early in the course of disease, it is usually possible to adjust the amount and timing of the doses of levodopa to control parkinsonian symptoms without inducing dyskinesias; however, as the disease advances and the therapeutic window narrows, cycling between on periods complicated by dyskinesia and off periods with resulting immobility is common. Eventually, despite adjustments in levodopa dose, many patients with advanced PD experience either mobility with severe dyskinesias or complete immobility. In most patients, this effect bears no clear relationship to the timing of the dose or levodopa serum levels. The wearing off or end-of-dose effect is a more predictable effect that occurs at the latter part of the dosing interval after a period of relief; it can be improved by various means such as shortening the dosing interval or by adjunctive therapy with a dopamine agonist (if not already present) or levodopa extender such as a COMT inhibitor.

The pathophysiologic basis for motor complications and dyskinesias is not entirely clear, but incomplete delivery of dopamine to central receptors is likely responsible. As the disease progresses, dopamine terminals are lost and the capacity to store dopamine presynaptically is diminished. This dopaminergic denervation impairs the ability to maintain striatal dopamine concentrations at a relatively constant level. As a consequence, dopamine receptors are subject to intermittent or pulsatile stimulation rather than by a more natural physiologic tonic stimulation. Overactivity of excitatory pathways mediated by neurotransmitters such as glutamate may also be involved. Variations in the rate and extent of levodopa absorption, dietary substrates...
Levodopa Drug Interactions

<table>
<thead>
<tr>
<th>Drug</th>
<th>Interaction</th>
<th>Mechanism</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anticholinergics</td>
<td>↓ Levodopa</td>
<td>Gastric emptying, thus ↓ degradation of levodopa in gut, and ↓ amount absorbed</td>
<td>Watch for ↓ levodopa effect when anticholinergics used in doses sufficient to ↓ GI motility. When anticholinergic therapy discontinued in a patient on levodopa, watch for signs of levodopa toxicity. Anticholinergics can relieve symptoms of parkinsonism and might offset the reduction of levodopa bioavailability. Overall, interaction of minor significance.</td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>↓ Levodopa</td>
<td>Mechanism unknown</td>
<td>Use together with caution; discontinue if interaction observed.</td>
</tr>
<tr>
<td>Ferrous sulphate</td>
<td>↓ Levodopa</td>
<td>Formation of chelation complex</td>
<td>Avoid concomitant administration.</td>
</tr>
<tr>
<td>Food</td>
<td>↓ Levodopa</td>
<td>Large, neutral amino acids compete with levodopa for intestinal absorption</td>
<td>Although levodopa usually taken with meals to slow absorption and ↓ central effects, high protein diets should be avoided.</td>
</tr>
<tr>
<td>MAOI (e.g., phenelzine, tranylcypromine)</td>
<td>↓ Levodopa</td>
<td>Peripheral dopaminergic and noradrenergic neurotransmission</td>
<td>Avoid using together; selegiline and levodopa used successfully together. Carbidopa might cause hypertensive reaction to levodopa in patients receiving an MAOI.</td>
</tr>
<tr>
<td>Methyl dopa</td>
<td>↑ or ↓ levodopa effect</td>
<td>Acts as central and peripheral decarboxylase inhibitor</td>
<td>Avoid using together.</td>
</tr>
<tr>
<td>Metoclopramide</td>
<td>↓ Levodopa</td>
<td>Central dopamine blockade</td>
<td>Avoid using together.</td>
</tr>
<tr>
<td>Neuroleptics (e.g., butyrophenones, phenothiazines)</td>
<td>↓ Levodopa</td>
<td>Central blockage of dopamine neurotransmission</td>
<td>Important interaction; avoid using these drugs together.</td>
</tr>
<tr>
<td>Phenothiazine</td>
<td>↓ Levodopa</td>
<td>Mechanism unknown</td>
<td>Avoid using together if possible.</td>
</tr>
<tr>
<td>TCA</td>
<td>↓ Levodopa</td>
<td>Peripheral decarboxylation of levodopa</td>
<td>Not observed when levodopa given with carbidopa.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Levodopa degradation in gut because of delayed emptying</td>
<td>TCA and levodopa have been used successfully together; use with caution.</td>
</tr>
</tbody>
</table>

GI, gastrointestinal; MAOI, monoamine oxidase inhibitor; TCA, tricyclic antidepressant.

(e.g., large neutral amino acids) that compete with cerebral transport mechanisms, levodopa drug–drug interactions (Table 57.4), and competition for receptor binding by levodopa metabolites can further explain the variable responses observed to levodopa.

**CASE 57.1, QUESTION 15**: What options are available to reduce L.M.’s motor fluctuations?

**CONTROLLED-RELEASE CARBIDOPA/LEVODOPA**

A more sustained delivery of levodopa than that achieved with routine oral dosing has been suggested to reduce motor complications, because it would more effectively replicate normal physiology. Several studies have documented the efficacy of continuous infusions of levodopa in patients with advanced PD, but this strategy is not widely used outside of research protocols. A controlled-release formulation of carbidopa/levodopa is available, containing 25 mg carbidopa and 100 mg levodopa or 50 mg carbidopa and 200 mg levodopa in an erodible polymer matrix that retards dissolution in gastric fluids. Although off time should theoretically be reduced by the slower rate of plasma levodopa decline, clinical study has generally not found a difference in off time, or a reduction in dyskinesias, with the controlled-release preparation compared with the immediate-release preparation. As a result, the American Academy of Neurology Practice Parameters for treatment of motor fluctuations and dyskinesias does not recommend switching to controlled-release carbidopa/levodopa as a primary strategy to reduce off time or lessen dyskinesias.

A likely reason for the lack of superior effect with controlled-release carbidopa/levodopa is its variable absorption. Controlled-release carbidopa/levodopa is about 30% less bioavailable than the immediate-release formulation. Patients converted from standard carbidopa/levodopa to the controlled-release formulation should receive a dose that will provide 10% more levodopa, and then the dose should be titrated upward to clinical response. Given that there is no obvious advantage to controlled-release carbidopa/levodopa, L.M.’s levodopa formulation should not be switched. Rather, L.M.’s condition may be improved by taking his immediate-release carbidopa/levodopa more frequently and avoiding substantial increases in the total daily dose, which could worsen his dyskinesias. Taking his morning dose before arising from bed may help with his early morning problems and prevent other response fluctuations. If L.M.’s symptoms are not improved with adjustment of his carbidopa/levodopa dose, a number of adjunctive agents such as dopamine agonists, apomorphine rescue, COMT inhibitors, and MAO-B inhibitors can be considered.

**DOPAMINE AGONISTS**

The effectiveness of pramipexole added to levodopa therapy in advanced PD was evaluated in a multicenter, placebo-controlled study of 360 patients with a mean disease duration of 9 years. Pramipexole was titrated gradually to the maximal effective dose as tolerated, and doses did not exceed 4.5 mg/day in three divided doses. At the end of a 6-month maintenance period, patients treated with pramipexole had a 22% improvement in their ADLs (p <0.0001) and a 23% improvement in their motor scores (p <0.0006). Dyskinesias and hallucinations were more common in pramipexole-treated patients, and nesiritide levodopa dose reduction in 76% of the pramipexole group compared with 14% in the placebo group. The total daily levodopa dose was decreased by 27% in those treated with pramipexole compared with 3% in the placebo group.
AMANTADINE

The antiviral agent, amantadine, was serendipitously found to improve PD symptoms in an uncontrolled, open-label, bilateral, randomized, double-blind, parallel-group study of 29 patients, compared with 13% of those in the placebo group. In a study of 208 PD patients not optimally controlled with levodopa after up to 3 years of therapy with less than 600 mg/day of levodopa, a prolonged-release, once-daily formulation of ropinirole was found to improve motor scores in a similar fashion to increasing the levodopa dose; however, only 3% of ropinirole-treated subjects experienced dyskinesias compared with 17% of levodopa-treated patients (p < 0.001).69 In moderate-to-advanced PD, treatment benefits were observed within 2 weeks of initiation.69

Because L.M. has advanced disease and is experiencing motor fluctuations despite a treatment regimen that includes a dopamine agonist, further dose adjustments of the dopamine agonist may provide little additional benefit. Any adjustments must be made with consideration of worsening dyskinesia and the possibility of exacerbating central nervous system adverse effects.

APOMORPHINE

Apomorphine is a dopamine agonist that is approved as rescue therapy for treatment of hypomobility or off episodes in patients with PD. It is available only in injectable form. In a randomized, double-blind, parallel-group study of 20 patients, rescue treatment with apomorphine resulted in a 34% reduction (~2 hours) in off time compared with 8% in the placebo group (p = 0.02).67 Mean UPDRS motor scores were reduced by 23.9 (p < 0.03). Because excess apomorphine administration can cause severe hypotension, it should be administered with an antiemetic such as trimethobenzamide. The antiemetic should be started 3 days before initiating apomorphine and continued for the first 2 weeks of treatment.70 Apomorphine should not be used with ondansetron or other serotonin antagonists used to treat nausea because the combination may cause severe hypotension. In addition, other antiepileptics, such as p-chlorophenazone and metoclopramide, should not be given concurrently with apomorphine because they are dopamine antagonists and can decrease the effectiveness of apomorphine.

Doses of apomorphine range from 2 to 6 mg per subcutaneous injection. A 2 mg test dose is recommended while monitoring blood pressure. If tolerated, the recommendation is to start with a dose of 1 mg less than the tolerated test dose, and increase the dose by 1 mg every few days if needed. Peak plasma levels are observed within 10 to 60 minutes after dosing, so the onset of therapeutic effect is rapid. Two main disadvantages of apomorphine are that the test dose and titration are time-consuming and must be done under physician supervision, and that patients may require someone else to inject the drug once hypomobility has occurred. For these reasons, apomorphine is not widely used. Given that L.M. is experiencing motor fluctuations almost daily, long-term frequent apomorphine use would not be a viable solution in his situation.
by preventing its peripheral degradation though inhibition of COMT.

Entacapone and tolcapone are selective, reversible, and potent COMT inhibitors that increase the amount of levodopa available for transport across the blood–brain barrier (Fig. 57-4). This effect prolongs the response to levodopa as measured by an increase in the amount of on time and a decrease in the daily levodopa dose. The pharmacologic and pharmacokinetic effects of entacapone and tolcapone are compared in Table 57-5. Tolcapone is slightly more potent and has a longer duration of action than entacapone. Entacapone is usually given with every administration of carbidopa/levodopa (up to eight tablets per day), whereas tolcapone is dosed three times daily. Tolcapone is associated with cases of fatal, acute fulminant liver failure, which has led to stringent liver function monitoring requirements and limited clinical use. If initiated, liver function monitoring should be performed at baseline and every 2 to 4 weeks for the first 6 months, followed periodically thereafter as clinically necessary. Because of the risks for hepatotoxicity associated with tolcapone, entacapone is the preferred COMT inhibitor and would be a good choice for L.M. if he desires an increase in his on time. Entacapone has a Level A evidence recommendation to reduce off time in the American Academy of Neurology Practice Parameter addressing the treatment of motor fluctuations and dyskinesias.

### ENTACAPONE

**CASE 57-1, QUESTION 16:** Six months after adjusting the frequency of his carbidopa/levodopa and adding amantadine, L.M. reports that his dyskinesias are not too bothersome, but he is having increased periods (lasting a few minutes) in which he cannot move. He is currently taking...
amantadine 100 mg twice daily, pramipexole 0.5 mg TID, and immediate-release carbidopa/levodopa 25/250 five times a day, but “even on a good day” gains symptomatic relief for only about 2 to 3 hours after a dose. The decision is made to initiate entacapone therapy and gradually discontinue pramipexole as symptoms or side effects demand. How effective is entacapone for reducing the symptoms of PD?

The efficacy and safety of entacapone as an adjunct to levodopa therapy was established in two pivotal multicenter, randomized, double-blind, placebo-controlled trials. Subjects for both studies had idiopathic PD with motor fluctuations, including wearing-off phenomena, despite maximal tolerated doses of levodopa. In the first study, 171 patients were randomly assigned to receive either entacapone 200 mg or placebo (4–10 doses per day) with each dose of carbidopa/levodopa. After 6 months, the mean on time per 18-hour period increased by 1.5 hours in the entacapone-treated group compared with the placebo-treated group (p < 0.001). Withdrawal of entacapone resulted in a return to baseline on time levels. Mean off time during an 18-hour day decreased by 1.2 hours in the entacapone-treated group compared with the placebo-treated group (p < 0.001). Improvements of approximately 10% to 20% in these motor scores usually produce clinically significant improvements as indicated by increased functional capacity and decreased parkinsonian symptoms (bradykinesia and rigidity). Patients who received entacapone could also lower their levodopa daily dose by an average of 79 mg, whereas placebo-treated subjects required an increase of 12 mg in their average daily levodopa dose (p < 0.001). A 3-year open-label extension of this trial demonstrated continued efficacy and tolerability of entacapone.

In the second study, 285 patients were randomly assigned to receive either entacapone 200 mg or placebo (up to 10 doses per day) with each dose of carbidopa/levodopa. At baseline, patients had experienced about 4 years of motor fluctuations and had been taking levodopa for about 9 years. Approximately 80% of the study subjects continued to take other antiparkinsonian therapies, including anticholinergic agents, selegiline, dopamine agonists, and amantadine. Compared with placebo over the course of 8 to 24 weeks, daily, on time increased by about 1 hour (p < 0.05) in patients treated with entacapone, with the greatest improvements observed in those who had a smaller percentage of on time at baseline. Those treated with entacapone also had about a 10% reduction in their total UPDRS scores, and they decreased their daily levodopa dose by about 100 mg (13%).

Dosing

CASE 57-1, QUESTION 17: When should entacapone be initiated, and what is the most effective method for dosing the drug? If initiated at the same time as levodopa, can it prevent the onset of levodopa-induced dyskinesias?

Entacapone is approved for use as adjunctive therapy to levodopa for the treatment of PD in patients experiencing wearing-off or end-of-dose deterioration. It is not necessary to titrate the dose; rather, it is given as one 200-mg tablet with each carbidopa/levodopa administration, up to eight tablets per day. It is available in a combination tablet with a 1:4 ratio of immediate-release carbidopa/levodopa that patients can be switched to once they are stabilized individually on carbidopa/levodopa and entacapone. If dyskinesias occur, it may be necessary to lower the levodopa dose by approximately 10% to 25%, particularly if the patient is receiving more than 800 mg/day of levodopa. Although pramipexole is being discontinued in L.M., he should still be monitored for dyskinesias, especially during the first few weeks of therapy, as it may also be necessary to lower his carbidopa/levodopa dose.

Early initiation of a COMT inhibitor from the time levodopa is first introduced has been proposed as a way of reducing the occurrence of levodopa-induced motor complications. Theoretically, such a strategy should provide more-stable plasma levels of levodopa and lessen pulsatile stimulation of striatal dopamine receptors normally observed with intermittent levodopa dosing. This strategy was recently tested in the Stalevo Reduction in Dyskinesia Evaluation in Parkinson’s Disease (STRIDE-PD) study, a multicenter, double-blind study that randomly assigned 747 patients to initiate either carbidopa/levodopa or carbidopa/levodopa/entacapone four times daily. Surprisingly, patients randomly assigned to receive carbidopa/levodopa/entacapone actually had a shorter time to onset of dyskinesia (hazard ratio, 1.29; p = 0.04) and increased dyskinesia frequency at week 114 (42% vs. 32%; p = 0.02). These findings may have been confounded by an increased use of dopaminergic therapy in the entacapone group or may reflect relatively unstable plasma levodopa levels given that levodopa was not delivered continuously. The findings of the STRIDE-PD study do not support the early administration of entacapone in combination with levodopa to reduce the occurrence of motor complications.

Adverse Effects

CASE 57-1, QUESTION 18: What are the adverse effects of entacapone, and how should they be managed?

Most entacapone-induced adverse effects are consistent with increased levodopa exposure. They include dyskinesias (50%–60%), nausea (13%–20%), dizziness (10%–25%), and hallucinations (1%–14%). Reducing the levodopa dosage by 10% to 15% as a strategy for circumventing these effects was successful in about one-third of patients experiencing dyskinesias. Other adverse effects related to entacapone include urinary discoloration (11%–40%), abdominal pain (6%), and diarrhea (10%). Urine discoloration (brownish-orange) is attributed to entacapone and its metabolites and is considered benign, but patients should be counseled regarding this effect to avoid undue concern. The most common reason for withdrawal from clinical studies and discontinuation of therapy was severe diarrhea (3.5%). No monitoring of liver function tests is required during entacapone therapy.

Recently, the Food and Drug Administration notified health care professionals that it is undertaking a meta-analysis to examine the cardiovascular risks associated with entacapone. This action was prompted by an evaluation of data from the STRIDE-PD study, which indicated that patients taking the combination carbidopa/levodopa/entacapone may be at an increased risk for cardiovascular events (heart attack, stroke, and cardiovascular death) compared with those taking carbidopa/levodopa.

Monoamine Oxidase-B Inhibitors

SELEGILINE AND RASAGILINE

CASE 57-2

QUESTION 1: K.B. is a 61-year-old woman who presents to the movement disorders clinic after referral from her family doctor for a presumptive diagnosis of PD. She is Hoehn
and Yahr stage 1, with slightly decreased arm swing on the left side and unilateral resting hand tremor. Her past med-
ical history is significant for hypertension and mild renal insufficiency (serum creatinine of 1.4 mg/dL), likely owing to the fact that she was born with only one functioning kidney. Since her initial visit with her family physician, she has been researching information about different PD treat-
ments from several PD-related websites. She is particularly interested today in learning more about possible neuropro-
tective effects of medications for PD. What role do MAO-B inhibitors have in the treatment of PD, and is there any evi-
dence for neuroprotection?

The development of effective disease-modifying therapies for PD is largely precluded by the inability to readily identify individ-
uals in the presymptomatic state. By the time patients present with motor symptoms, substantial neuropathology has accu-
ulated during the long preclinical evolution of the disease; an ability to recognize PD at an earlier stage would be a major break-
through. A number of agents have exhibited neuroprotective effects in animal models, but none have had a clear impact on clinical outcomes in human studies.49

SELEGILINE
Selgeline (also referred to as deprenyl) is an irreversible inhibitor of MAO type B, a major enzymatic pathway responsible for the metabolism of dopamine in the brain.50 The discovery of MPTP fostered the development of animal models in which it was found that the neurotoxicity associated with MPTP is not directly caused by MPTP itself, but rather the oxidized prod-
uct, 1-methyl-4-phenylpyridinium (MPP).62 The conversion to MPP is a two-step process mediated in part by MAO-B. Inhibi-
tion of MAO-B can inhibit the oxidative conversion of dopamine to potentially reactive free radicals.63 In animals, pretreatment with selegiline protects against neuronal damage after the adminis-
tration of MPTP.64 The Deprenyl and Tocopherol Antioxidative Therapy of Parkinsonism (DATATOP) study was designed to test the hypoth-
esis that the combined use of selegiline and an antioxidant (α-tocopherol) early in the course of the disease may slow disease progress-
ion.65 The primary outcome was the length of time that patients could be sustained without levodopa therapy (an indica-
tion of disease progression). Early treatment with selegiline 10 mg/day delayed the need to start levodopa therapy by approx-
imately 9 months compared with patients given placebo; however, long-term observation showed that the benefits of selegiline were not sustained and diminished with time. During an addi-
tional year of observation, patients originally randomly assigned to selegiline tended to reach the end point of disability even more quickly than did those not assigned to receive selegiline. Initial selegiline treatment did not alter the development of levodopa’s adverse effects such as dyskinetasias and wearing-off and on-off phenomena.

Although selegiline does not appear to have neuroprotective effects in humans, it may have a role as a symptomatic adjunct to levodopa in more advanced disease. Studies have found improve-
ment in the wearing off effect of levodopa in 50% to 70% of patients treated with selegiline and a reduction in as much as 50% in the total daily dose of levodopa.63,66 The on-off effect is less responsive to the addition of selegiline.

Selegiline is available in a 5-mg capsule or tablet, and as a 1.25-mg mini-oral disintegrating tablet. It is also available in a trans-
dermal patch, but this formulation is not approved for use in PD (approved for treatment of depression). The bioavail-
ability of conventional selegiline is low, and it undergoes extensive hepatic first-pass metabolism into amphetamine-based metabo-
lites, which have been hypothesized to be neurotoxic.67 The usual dosage of conventional selegiline is 10 mg/day given in 5-mg doses in the morning and early afternoons. It is not given in the evening because excess stimulation from metabolites (1-methamphetamine and 1-amphetamine) can cause insomnia and other psychiatric side effects.68 The orally disintegrating tablet formulation dissolves in the mouth on contact with saliva and undergoes pregastric absorption. This is an improvement over conventional selegiline because it minimizes the effect of first-pass metabolism and results in higher plasma concentra-
tions of selegiline and reductions in the amphetamine-based metabolites.69 Indeed, this formulation was shown to reduce off

time by 32% (2.2 hours) compared with 9% (0.6 hours) for placebo in a 2-week, randomized, multicenter, parallel group, double-
blind study.68 Because selegiline selectively binds to MAO-B in

usual doses (≤10 mg/day), it does not produce a hypertensive reaction (“cheese effect”) with dietary tyramine or other cate-
cholamines. It is still recommended, however, that patients be counseled regarding this potential risk.

RASAGILINE
Rasagiline is a second-generation, propargylamine-type irre-
versible selective inhibitor of MAO-B. It is indicated as mono-
thrapy in early disease or as adjunct therapy to levodopa in advanced disease. Rasagiline is differentiated from selegiline primarily in

that it is a more potent inhibitor of MAO-B, and it is not metab-
olized into amphetamine-based metabolites.70 Like selegiline, rasagiline has also been found to protect from MPTP-induced parkinsonism in animal models.70,71

Rasagiline was studied as monotherapy in early PD in a randomized, double-blind, placebo-controlled trial comparing rasagiline 1 mg (n = 114) or 2 mg (n = 132) daily with placebo (n = 118). After 6 months of therapy, the mean adjusted change in UPDRS scores compared with placebo were −4.2 and −3.56 in the 1- and 2-mg groups, respectively (p <.001 for both).71 These changes are quantitatively similar to those observed with lev-
odopa therapy. This study used a delayed-start design, wherein at the end of the initial 6 months of treatment, patients who received placebo were then switched over to receive active treat-
ment with rasagiline, and the rasagiline-treated patients contin-
ued on therapy. After an additional 6 months of study, it was found that patients receiving rasagiline for all 12 months had less func-
tional decline than patients in whom rasagiline was delayed.71 The mean adjusted difference at 12 months for patients receiv-

ing rasagiline 2 mg/day for all 12 months was −2.29 compared with the delayed-start rasagiline 2-mg group (p = 0.01). These encouraging findings suggested that neuroprotection might be afforded by rasagiline, and prompted a larger, more definitive study.

The Attenuation of Disease Progression with Azilect Given Once-daily (ADAGIO) study was conducted in follow-up to the earlier findings that suggested the possibility of neuroprotection with rasagiline. This was also a randomized, placebo-controlled trial using the delayed-start methodology, but with a much larger sample size (n = 1,176).72 Patients were randomly assigned to receive rasagiline (either 1 or 2 mg/day) or placebo for 36 weeks. At 36 weeks, rasagiline-treated subjects continued therapy, and the placebo group was switched to either 1 or 2 mg/day of rasagi-
line; all patients were then followed for an additional 18 weeks. To prove disease modification attributable to rasagiline with either dose, the early-start treatment group had to meet each of three hierarchical end points, based on magnitude and rate of change of UPDRS scores during different periods of the study. At the end of the study, the early-start group receiving rasagiline 1 mg/day met all end points, suggesting a possible disease-modifying effect, but
the 2-mg dose failed to meet all three of the required end points. The inconsistency between doses led the authors to state that they could not definitively conclude that rasagiline 1 mg/day has disease-modifying effects.106

Rasagiline has also been studied as an adjunct to levodopa in advanced disease. When added to levodopa therapy, rasagiline can improve motor fluctuations, reducing off time by 1.4 hours and 1.8 hours compared with 0.9 hours for placebo (p = 0.02 and p = 0.0001 for 0.5- and 1-mg/day groups, respectively).107 Significant improvements were reported in the UPDRS subscores for ADLs in the off state and motor performance in the on state, as well as clinician global assessments. Dyskinesias were slightly worsened in the 1-mg/day group. As adjunctive therapy to levodopa, rasagiline appears to provide similar benefit to entacapone, and is also given a Level A evidence rating for reducing off time in the Practice Parameter addressing motor fluctuations and dyskinesias.108 When compared with entacapone 200 mg administered with each levodopa dose, rasagiline 1 mg/day reduced total daily off time in a similar manner (decrease of 21% or 1.18 hours for rasagiline and 21% or 1.2 hours for entacapone).109

Rasagiline is available in 0.5- and 1-mg tablets. When used as monotherapy, it is initiated at 1 mg daily. When combined with levodopa, the initial dose is lowered to 0.5 mg daily, and can be increased to 1 mg daily based on response. Although tyramine-challenge studies have not demonstrated any clinically significant reactions, the product labeling still contains a warning that patients should be advised to restrict tyramine intake.109,110 Rasagiline is well-tolerated, headache, dizziness, and nausea appear to be the most common adverse effects when rasagiline is given as monotherapy.110 Reduction of levodopa dose may be necessary if dyskinesia occurs when rasagiline is added in combination to levodopa. Similar precautions regarding drug interactions exist with rasagiline as selegiline, that is, sympathomimetics, meperidine, dextromethorphan, other MAO inhibitors, and selective serotonin reuptake inhibitors (SSRIs) should be avoided or used with caution. Because rasagiline is metabolized by CYP1A2, inhibitors such as ciprofloxacin may increase plasma concentrations of rasagiline.

The search for agents capable of clinically apparent neuroprotection remains a primary focus in the management of PD. The disappointing legacy of selegiline and the ambiguity of the ADAGIO study results with rasagiline underscore the fact that overt and tangible neuroprotective effects of PD therapies remain elusive. Nevertheless, given the efficacy of rasagiline in early disease, it would be a reasonable agent to try in a patient such as K.B. who presents very early in her disease course and seeks a possible neuroprotective agent. Depending on her degree of functional impairment caused by the tremor, additional therapy may be necessary.

Anticholinergics

CASE 57.2, QUESTION 2: Should K.B. receive an anticholinergic agent? What role do anticholinergic drugs play in the treatment of PD?

Anticholinergic drugs have been used to treat PD since the mid-1800s, when it was discovered that symptoms were reduced by the belladonna derivative hyoscyamine sulfate (scopolamine).112 These drugs work by blocking the excitatory neurotransmitter acetylcholine in the striatum, which minimizes the effect of the relative increase in cholinergic sensitivity. Until the late 1960s, when amantadine and levodopa were introduced, anticholinergics were a mainstay of treatment; however, because of their undesirable side effect profile and poor efficacy relative to levodopa in treating bradykinesia and rigidity, anticholinergic agents are no longer used as first-line agents. Instead, they are usually reserved for the treatment of resting tremor early in the disease, particularly in younger patients with preserved cognitive function. Given her history and clinical presentation, K.B. would probably benefit from an anticholinergic drug such as trihexyphenidyl 1 mg/day.

K.B. should be observed carefully for adverse effects on initiation of an anticholinergic. These drugs produce both peripherally and centrally mediated adverse effects. Peripheral effects, such as dry mouth, blurred vision, constipation, and urinary retention, are common and bothersome.113 Anticholinergic agents can increase intraocular pressure and should be avoided in patients with angle-closure glaucoma. Central nervous system effects can include confusion, impairment of recent memory, hallucinations, and delusions.114 Patients with PD are more susceptible to these central effects because of advanced age, intercurrent illnesses, and impaired cognition.115 As K.B.’s disease eventually progresses and she develops other nonmotor complications, the benefit versus risk of anticholinergic therapy should be periodically re-evaluated.

Antioxidants

CASE 57-2, QUESTION 3: Are there any antioxidants, dietary supplements, or other investigational therapies that may benefit K.B.?

Antioxidants have been hypothesized to benefit patients with PD through their ability to act as free radical scavengers. The most comprehensive evaluation of antioxidant therapy for PD comes again from the DATATOP study.116,117 In this study, patients were assigned to one of four treatment regimens: alpha-tocopherol (2,600 international units/day) and entacapone placebo, selegiline 10 mg/day and alpha-tocopherol placebo; selegiline and alpha-tocopherol active treatments; or dual placebo. The primary end point was time to requirement of levodopa therapy. After approximately 14 months of follow-up, no difference was seen between the selegiline group and placebo group in time to require levodopa.116 Thus, despite the theoretic benefit, clinical data are lacking to support the routine use of alpha-tocopherol, and it would not be recommended in K.B.117

COENZYME Q10

Coenzyme Q10 (CoQ10) is an antioxidant involved in the mitochondrial electron transport chain, and has been shown to have reduced levels in patients with PD.118 The finding that MPTP can induce parkinsonism through inhibition of complex I in the mitochondrial electron transport chain led to the hypothesis that supplementation with CoQ10 may help restore dysfunctional mitochondria.119 Early results in a trial of 80 patients with untreated PD, randomly assigned to placebo or CoQ10 at dosages of 300, 600, or 1,200 mg/day in four divided doses, were promising.120 Subjects were followed for up to 16 months or until therapy with levodopa was required. The primary outcome was a change in total score on the UPDRS from baseline to the last visit. Total UPDRS scores increased (indicating worsening of symptoms) to a greater extent in placebo-treated patients than in those treated with CoQ10 (+11.99 for placebo, +9.81 for 300 mg/day, +10.82 for 600 mg/day, and +6.69 for 1,200 mg/day). A larger study was undertaken in follow-up, using a futility design, randomly assigning 213 untreated PD patients to CoQ10 600 mg four times daily or placebo.119 The primary outcome

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measure was the mean change in total UPDRS score from baseline to either the time required for symptomatic therapy or 12 months, whichever came first. The threshold value for futility of CoQ10 was defined as 30% less progression on the total UPDRS than the 10.65-unit change observed historically in the placebo arm of the DATATOP trial, or 7.46. After 12 months of therapy, the mean change in the CoQ10 group was 7.52 compared with 6.31 in the placebo group. Based on the prespecified criteria, although CoQ10 did not meet the prespecified end point of a change of 7.46 or less, it could not be rejected as futile and met criteria for further clinical testing. Further testing of CoQ10 in phase 3 trials is currently being conducted. In the meantime, given the small likelihood of harm from CoQ10, K.B. can be counseled about the possibility for modest benefits and advised to make an informed decision about using it.

**CREATINE AND MINOCYCLINE**

Similar to the theory for efficacy of CoQ10, creatine plays a role in mitochondrial energy production and has been shown to protect from MPTP-induced dopamine depletion in animal models. Minocycline is an anti-infective agent that also displays anti-inflammatory effects, and is hypothesized to alter the neuroinflammatory response that occurs as dopaminergic neurons are lost in PD. Minocycline has been shown to be protective in MPTP animal models of PD. The use of both creatine and minocycline in PD was examined in a futility-design study, in which 268 patients with early PD not requiring therapy were randomly assigned to receive creatine (n = 67) 10 g/day, minocycline 200 mg/day (n = 66), or placebo (n = 67). The study was identical in design to the CoQ10 study discussed previously and used the same primary end point. After 12 months, the mean change in the total UPDRS was 9.6 units in the creatine group, 7.09 in the minocycline group, and 8.39 in the placebo group. Based on the prespecified criteria, neither creatine nor minocycline could be rejected as futile and met criteria for further clinical testing. Additional studies of these agents are currently ongoing. Given the unresolved issues surrounding the induction of antibiotic resistance with long-term use of an agent such as minocycline, it should be avoided in K.B. Likewise, given her mild renal insufficiency, she should also be advised to avoid creatine.

**Surgical Therapies for PD**

**CASE 57.3**

**QUESTION 1:** S.L. is a 68-year-old man with a 10-year history of PD, now considered to be in Hoehn and Yahr late stage 3. His current regimen includes sustained-release carbidopa/levodopa 50/200 mg twice daily, immediate-release carbidopa/levodopa 25/100 mg TID, ropinirole 2 mg TID, and amantadine 100 mg twice daily. S.L.’s overall control of his PD has diminished greatly in the last couple of months. His on time averages around 6 hours/day, with the majority of it accompanied by troublesome dyskinesias. Most days he needs some assistance with ADLs. His cognitive function remains well preserved, and he is not depressed. He has heard about surgical procedures that might benefit patients with PD. Is surgical therapy superior to medical therapy in patients with advanced PD?

Two types of surgical therapies have been used in patients with advanced PD who cannot be adequately controlled with medications. The first involves making an irreversible surgical lesion in a specific location in the brain (e.g., posteroventral pallidotomy or stereotactic thalamotomy); the second involves surgical implantation of a device that sends electrical impulses to specific parts of the brain (e.g., deep brain stimulation [DBS]). Deep brain stimulation. A pulse generator, surgically implanted in a pouch beneath the clavicle, sends high-frequency electrical impulses to the thalamus, thereby blocking the nerve pathways associated with tremors in Parkinson disease. Adapted with permission from Smeltzer SC, Bare BJ. Textbook of Medical-Surgical Nursing, 9th ed. Philadelphia, PA: Lippincott Williams & Wilkins, 2000.
Additionally, 71% of patients receiving DBS experienced clinically meaningful motor function improvements (≥3-point change in UPDRS motor score) compared with only 32% of patients receiving best medical therapy (p < 0.001).118 At the end of the 6 month assessment, all patients (including those originally randomly assigned to best medical care) proceeded to DBS with random assignment to STN or GPi targets, and outcomes were evaluated at 24 months.119 There were no significant differences in the change in UPDRS motor score between those receiving DBP targeting the STN and those with the GPi targeted (p = 0.05). However, secondary outcomes revealed some minor between group differences; those undergoing DBS targeting the STN required lower doses of dopaminergic agents (p = 0.02), and those receiving DBS targeting the GPi had less decline in visuomotor processing speed (p = 0.03), greater improvement in depression (p = 0.02), and fewer adverse events (31% vs. 56%, p = 0.03).118

CASE 57.3, QUESTION 2: What surgical therapy would be most appropriate for S.L.?

S.L. appears to be an ideal candidate for DBS. Candidates for DBS should have idiopathic PD and be levodopa-responsive, but continue to experience motor complications or tremor despite optimal pharmacotherapeutic regimens. Ideally, DBS should be avoided in patients with pre-existing cognitive or psychiatric problems owing to a slight risk of decline in cognition. No strict age limitation for DBS exists, but patients younger than 70 years of age, such as S.L., appear to recover from surgery more quickly and show greater motor improvements. Although both the GPi and STN would be acceptable targets of therapy in S.L., nonmotor factors may be considered when selecting the surgical target for DBS. DBS of the STN consistently demonstrates marked reduction in the need for escalating levodopa dosages compared with DBS of the GPi.120,121 but the results of the most recent comparative trial suggest other nonmotor symptoms may be affected more favorably when targeting the GPi.122

Treatment of Nonmotor Symptoms of Parkinson Disease

Although PD is mostly recognized for its cardinal features of motor dysfunction, nonmotor symptoms are an important part of the disease throughout all stages and a key determinant of quality of life.123 More than 98% of patients with PD have at least one nonmotor symptom; the average per patient is nearly eight, with the number and impact increasing in parallel with disease duration and severity.123 Common nonmotor symptoms include autonomic dysfunction (gastrointestinal disorders, orthostatic hypotension, sexual dysfunction, urinary incontinence), sleep disorders (restless leg syndrome, periodic limb movements of sleep, excessive daytime somnolence, insomnia, rapid eye movement (REM) sleep behavior disorder), fatigue, and anxiety.123 In one longitudinal study of patients with PD, the most common nonmotor symptoms were psychiatric symptoms (80%, most commonly anxiety), fatigue (58%), leg pain (38%), insomnia (32%), urinary symptoms (33%), drooling (31%), and difficulty concentrating (31%).124 The management of several commonly encountered nonmotor symptoms are reviewed below. Table 57.6 summarizes pharmacological treatments for several nonmotor symptoms of PD.

| Table 57-6 | Summary of Pharmacological Treatments for Common Nonmotor Symptoms of Parkinson Disease |
|---|---|---|---|
| Domain | Symptom | Possible Treatments | Adverse Effect Considerations |
| Cognitive | Dementia | Rivastigmine, donepezil | Deterioration of motor function (tremor), salivation, excessive lacrimation, incontinence, nausea, vomiting, and orthostasis |
| Psychiatric | Depression | Dopamine agonists (pramipexole), TCAs (amitriptyline, desipramine, nortriptyline), SSRI s (citalopram, paroxetine) | Impulse control disorders (dopamine agonists); anticholinergic adverse effects (TCAs) on cognition, urinary symptoms, autonomic nervous system (orthostasis, falls), tremorgenic (SSRIs) |
| Anxiety | Benzodiazepines | | Decreased attention, cognition; increased risk of falls |
| Psychosis | Clozapine, quetiapine | | White cell count monitoring for clozapine (granulocytopenia) |
| Autonomic | Falls | If possible, avoid using medications that increase risk of falls | N/A |
| Erectile dysfunction | Sildenafil | | N/A |
| Constipation | Polyethylene glycol, fiber, stool softeners | | N/A |
| Orthostatic hypotension | Midodrine, fludrocortisone | | Focal weakness |
| Sleep | Excessive daytime sleepiness | Modafinil | Hypertension, pinnopexenia (midodrine) |
| Insomnia | Melatonin, benzodiazepines | | Dizziness, insomnia, anxiety |
| Periodic limb movements of sleep | Carbipoda/levodopa, dopamine agonists | Sedation, diaphoresis, falls, anxiety, cognitive dysfunction (benzodiazepines) |
| Miscellaneous | Fatigue | Methylphenidate | Impulse control disorders, psychosis |

N/A, not applicable; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant.
CASE 57-4, QUESTION 2: How should J.D.’s anxiety and depression be treated?

Despite being one of the strongest predictors of quality of life in PD patients, depression is often poorly recognized and inadequately treated.152-154 This is likely because the fact that depression and PD share overlapping features that often confound the identification of depression. Such features may include withdrawal, lack of motivation, flattened affect, decreased physical activity, or bradyphrenia.155-157 Treatment of depression in PD should first focus on providing adequate treatment of the symptoms of PD by attempting to restore mobility and independence, particularly in patients whose depression can be attributed to lengthy off periods. Antiparkinson drugs, such as pramipexole, can be associated with mood-enhancing effects independent of their ability to reduce time in the off state.158,159 Small trials and case reports have shown that depression in patients with PD can be successfully treated with antidepressant drugs, including tricyclic agents such as amitriptyline, desipramine, nortriptyline, bupropion, and SSRIs such as citalopram and paroxetine.127,131,133-136 Given the overall lack of controlled trials, it is difficult to know whether expected benefits reflect class responses or are unique to the individual agents studied. Importantly, the potential for adverse effects should always be considered when selecting an antidepressant in PD. For example, some SSRIs, such as fluoxetine, can be activating. Although this may be beneficial in patients who are apathetic or withdrawn, it may worsen symptoms in patients with PD who are agitated.134,135 With tricyclic antidepressants, care must be taken to observe for anticholinergic side effects that may worsen PD symptoms, such as impaired cognition, delayed gastric emptying (which may reduce levodopa effectiveness by increasing levodopa degradation in the gut), urinary problems, orthostatic hypotension, and increased risk of falls. Short-term use of benzodiazepines, such as lorazepam or alprazolam, may also provide relief of anxiety symptoms,160 but must be used cautiously owing to adverse effects on cognition and risk of falling. Generally, anxiety symptoms should improve with treatment of the underlying depression.

PSYCHOSIS

The incidence of psychotic symptoms increases with age and cognitive impairment in patients with PD. Other risk factors include higher age at PD onset, high doses of dopaminergic drugs, and REM sleep behavior disorder.158 Symptoms are often more pronounced at night (the “sundowning” effect), and hallucinations are typically visual. As with the management of cognitive impairment, it is important to eliminate or minimize any potential causative factors, particularly anticholinergic medications that could be contributing to the hallucinations or delirium. In some patients, reducing the dose of levodopa improves mental function and also provides satisfactory control of motor features. If it is not possible to achieve a balance between preserving motor control...
and decreasing neuropsychiatric symptoms through reduction in levodopa dosage, antipsychotics may be considered.

Older antipsychotic medications, such as haloperidol, perphenazine, and chlorpromazine, block striatal dopamine D₂ receptors and may exacerbate parkinsonian symptoms. Therefore, these agents are not recommended. 14 Newer atypical antipsychotics are more selective for limbic and cortical D₂, D₃, D₄ receptors; they have minimal activity at D₃ receptors and may control symptoms without worsening parkinsonism. Of these agents, clozapine has the best evidence of efficacy in patients with PD without adversely affecting motor function, and should be preferentially considered. 15,16 However, its use is complicated by the need for frequent monitoring of white blood cell counts because of the risk of agranulocytosis. Other newer agents, particularly quetiapine, appear promising and have controlled psychosis without worsening parkinsonism. 108,110 Risperidone and olanzapine have also been studied, but both worsened parkinsonism and were inferior to clozapine in patients with PD. 14,143 

Aripiprazole, also a newer atypical antipsychotic, has been associated with worsening motor function in patients with PD, whereas experience with ziprasidone has yielded mixed results. 144

**AUTONOMIC DYSFUNCTION**

Patients with PD frequently experience dysautonomia, including orthostasis, erectile dysfunction, constipation, nocturia, sensory disturbances, dysphagia, seborrhea, and thermoregulatory imbalances. Management of these symptoms is generally supportive, and appropriate medical interventions similar to those used in other geriatric patients can be used to treat these symptoms whenever encountered. In some cases, fluidrocortisone or midodrine can be considered if orthostatic hypotension is severe, although they have been subject to little study in PD patients specifically. 144 Other possibly effective treatments for symptoms of autonomic dysfunction outlined in the American Academy of Neurology Practice Parameter include sildenafil for erectile dysfunction and polyethylene glycol for constipation. 144

**FALLS**

Patients with PD and their caregivers should be counseled on the prevention of falls because they can result in serious morbidity and mortality. Falls generally result from one of several factors, including postural instability, freezing and festination, levodopa-induced dyskinesia, symptomatic orthostatic hypotension, coexisting neurologic or other medical disorders, and environmental factors. 145 Prevention remains the best strategy and includes environmental precautions, such as proper lighting, use of handrails, removing tripping hazards, and incorporating physical and occupational therapy. Reversible causes of postural or gait instability should be addressed whenever suspected.

**SLEEP DISORDERS**

Parasomnias often experienced by elderly persons are accentuated in PD patients. 14 Insomnia, sleep fragmentation owing to PD symptoms, restless leg syndrome, and REM sleep disorder (characterized by vivid dreams that are often acted out, especially if frightening) are common and a source of decreased quality of life. When sleep dysfunction can be directly attributed to PD symptoms, such as akinesia, tremor, dyskinesia, or nightmares, dosage adjustment of dopaminergic medications is indicated. Proper sleep hygiene should be encouraged. Short-acting benzodiazepines can be used if insomnia occurs; however, a longer-acting agent or controlled release formulation may be preferred if the patient wakes early and is unable to return to sleep. If excessive daytime drowsiness occurs, modafinil may be considered. 146 Similar to dysautonomia, management of sleep disorders that are not directly attributable to PD symptoms can be managed supportively, as in other geriatric patients.

**RESTLESS LEG SYNDROME AND PERIODIC LIMB MOVEMENTS OF SLEEP**

**Clinical Presentation**

**CASE 57-5**

**QUESTION 1:** J.J., a 47-year-old woman, presents to her family physician complaining of daytime fatigue and difficulty sleeping at night because of “jumpy legs.” She reports being able to sleep only 4 to 5 hours per night because of the leg restlessness, and feels unrefreshed after sleep. On further questioning, she describes the sensation in her legs as being like “bugs crawling under the skin.” The sensation is not painful. She explains that the symptoms worsen in the evening and at night and are partially relieved with walking. She recalls that her mother had similar symptoms. J.J.’s spouse notes that she often “kicks” him in her sleep. Review of her medical history shows an otherwise healthy postmenopausal woman. What signs and symptoms are suggestive of restless legs syndrome (RLS) in J.J.? What laboratory tests or diagnostic procedures should be performed in J.J. to evaluate her condition?

Restless legs syndrome, also known as Ekbom disease, is a disabling sensorimotor disorder estimated to affect approximately 2% of the adult population. 147 Although most patients with mild symptoms will not require treatment, RLS can be associated with adverse health outcomes, including sleep onset insomnia, missed or late work, anxiety, depression, marital discord, and even suicide in severe cases.

Four essential criteria have been established by the International Restless Legs Syndrome Study Group to diagnose RLS (Table 57-7). 148 The pathognomonic trait of RLS is an almost irresistible urge to move the legs (akathisia), often associated

### Table 57-7: Clinical Features of Restless Legs Syndrome

<table>
<thead>
<tr>
<th>Essential Criteria</th>
<th>Supportive Clinical Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urge to move legs, associated with paresthesias or dysesthesias</td>
<td>Accompanying sleep disturbance (sleep-onset insomnia)</td>
</tr>
<tr>
<td>Relief of symptoms with movement</td>
<td>Periodic leg movements</td>
</tr>
<tr>
<td>Onset or exacerbation of symptoms at rest</td>
<td>Positive response to dopaminergic therapy</td>
</tr>
<tr>
<td>Onset or worsening of symptoms during nighttime</td>
<td>Positive family history of RLS</td>
</tr>
<tr>
<td>Supportive clinical features</td>
<td>Otherwise normal physical examination</td>
</tr>
<tr>
<td>RLS, restless legs syndrome</td>
<td>RLS, restless legs syndrome</td>
</tr>
</tbody>
</table>

For a brief video summarizing the clinical features of a patient with PD, go to http://thepoint.lww.com.
with uncomfortable paresthesias or dysesthesias felt deep inside the limbs. Patients describe the sensation as “creepy-crawly” or “like tiny insects in the veins.” The symptoms may occur unilaterally or bilaterally, affecting the ankle, knee, or entire lower limb. With progressive disease, symptoms can begin earlier in the day, and progressive involvement of the arms or trunk may occur. Temporary or partial relief of symptoms can be achieved with movement. If patients attempt to ignore the urge to move the legs, akathisia will progressively intensify until they either move their legs or the legs jerk involuntarily. 1-3 Symptoms typically manifest in a circadian pattern with onset or worsening during nighttime hours (usually between 6 pm and 4 am, with peak symptoms between midnight and 4 am). The circadian pattern persists even in patients with inverted sleep-wake cycles. As a result of their symptoms, patients with RLS become “nightwalkers,” spending significant time walking, stretching, or bending the legs in an effort to relieve symptoms.

J.J.’s case is an example of a classic presentation of RLS. The prevalence of RLS increases with age and appears to be slightly more common in women. 8 She describes “creepy-crawly” sensations that are relieved partially with walking, a core feature of RLS. Her symptoms are worse during the evening hours. J.J. reports her mother suffered from similar symptoms. The observation of a familial tendency suggests a genetic component, and several chromosomal loci have been linked to the disease. 9 A strong family history of RLS appears to correlate with an early age of onset (<45 years), whereas presentation at a later age is associated with more neuropathy and accelerated disease progression. 10

Most cases of RLS are considered primary or idiopathic; therefore, the diagnosis does not require elaborate laboratory tests or diagnostic procedures. Several conditions are associated with RLS, and include iron deficiency, pregnancy, and end-stage renal disease. A thorough medical history should be taken in J.J. to rule out reversible causes of RLS or other conditions with similar characteristics. Several medications and substances are known aggravators of RLS, including medications with antidopaminergic properties, such as metoclopramide and prochlorperazine. Nicotine, caffeine, and alcohol can aggravate RLS through their own ability to interfere with quality of sleep. Additionally, SSRIs, tricyclic antidepressants, and commonly used over-the-counter antihistamines, such as diphenhydramine, can trigger or worsen RLS symptoms. 11 Hypotensive akathisia, leg cramps, and other conditions such as arthritis, which can cause positional discomfort with extended periods of sitting in one position, can mimic RLS. These conditions are easily distinguished from RLS because they are usually localized to certain joints or muscles, do not have a circadian pattern, and are not associated with an uncontrollable urge to move. With an otherwise unremarkable physical examination and medical history, specific laboratory tests that should be performed in J.J. are limited to serum ferritin and percent transferrin saturation (total iron binding capacity) to rule out iron deficiency anemia. It is important to note that ferritin is an acute-phase reactant and may be artificially elevated if there is an underlying inflammatory or infectious condition. Therefore, the ferritin level should always be accompanied by the percent transferrin saturation. Several studies have documented a relationship between low ferritin concentrations and increased symptoms severity. 12,13 J.J. is postmenopausal, so a pregnancy test is not necessary. Polysomnography is not usually indicated unless there is clinical suspicion for sleep apnea or if sleep remains disrupted despite treatment of RLS. When clinical suspicion from the physical examination or medical history suggests a possible peripheral nerve or radiculopathy cause, a routine neurologic panel, including thyroid function tests, fasting glucose, vitamins B6 and B12, and folate, should be obtained. 14 Renal function tests (serum creatinine and blood urea nitrogen) can be obtained to screen for uremia, although RLS does not usually occur in this situation until the patient has reached end-stage renal failure.

In addition to the presence of RLS, J.J.’s spouse has noticed what are likely PLMS. PLMS, also known as nocturnal myoclonus, are best described as involuntary clonic-type movements of the lower extremities while sleeping that usually involve bilateral ankle dorsiflexion, knee flexion and hip flexion. Approximately 80% of patients with RLS will also have PLMS, but PLMS can occur by itself and is also associated with significant sleep dysfunction. The diagnosis of PLMS usually requires a polysomnogram; the universally accepted criteria for diagnosis are that there should be at least four periodic leg movements (PLMs) in a 90-second period, with contractions typically lasting 0.5 to 2 seconds and recurring every 5 to 90 seconds. 15 A PLM index (PLMI) is calculated by dividing the total number of PLMs by sleep time in hours; an index of more than 5 but less than 25 is considered mild, a PLMI of more than 25 and less than 50 is moderate, and a PLMI of more than 50 is severe. The diagnosis of PLM disorder can be made when patients present with insomnia, tiredness, and daytime sleepiness in the presence of a high PLMI. 16 There is considerable overlap in the treatments of PLMS and RLS. Because J.J. clearly has RLS there is no need to perform a polysomnogram. The diagnosis of PLMS in her case is incidental and would not alter the clinical management. An exception to this would be if J.J.’s medical history revealed the possibility of sleep apnea, as there is a high association between PLMS and upper airway resistance146; a polysomnogram would then be indicated.

**CASE 57-5, QUESTION 2: What is the difference between RLS and periodic limb movements of sleep (PLMS)?**

Figure 57-6 presents an approach to the treatment of RLS. Iron supplements can potentially cure RLS symptoms in patients found to be iron deficient. 17 If J.J. is iron deficient, she should be prescribed 10 to 65 mg of elemental iron one to three times daily on an empty stomach with 200 mg of vitamin C to enhance absorption. After ruling out possible reversible causes of RLS, it is important to establish the frequency of J.J.’s symptoms and whether or not they are associated with pain. This information will help determine appropriate therapy.

Several classes of medications are effective for treating RLS. 18 Dopaminergic therapies are most consistently effective in relieving RLS symptoms, improving sleep, and reducing leg movements. The available dopaminergic therapies that have been evaluated in RLS include carbidopa/levodopa, pramipexole, ropinirole, bromocriptine, and rotigotine (not currently available in the United States). 19-22 Dopaminergic agonists are now the preferred dopaminergic class to treat RLS because they are longer acting than levodopa, which allows for more sustained efficacy and control of symptoms throughout the entire night. J.J. should be started on either ropinirole (0.25 mg initially, up to 0.5-4.0 mg/day) or pramipexole (0.125 mg initially, up to 0.5-1.5 mg/day), as both are both Food and Drug Administration-approved for treating RLS. Several randomized, controlled clinical trials have demonstrated benefit for patients with RLS treated with these medications.
documented efficacy of these agents in both objective and subjective ratings of improvement by patients and clinicians with either short- or long-term use.\textsuperscript{158–162} Ropinirole and pramipexole do not appear to differ with regard to efficacy or adverse effects. When used for RLS, ropinirole and pramipexole should be administered 2 hours before bedtime. Adverse effects are similar to those seen with the use of these agents in PD, and patients should be counseled accordingly.

Other medications may also provide modest benefit in RLS, including benzodiazepines, opiates, anticonvulsants, and clonidine.\textsuperscript{156} With the exception of gabapentin or opiates,\textsuperscript{163,164} which could be considered initially if J.J.’s discomfort was primarily caused by pain, all are considered to be alternatives to the dopaminergics. The dosing and adverse effects of the benzodiazepines used in RLS are similar to their use in the general population. No evidence suggests that one benzodiazepine is more effective than another for RLS, and selection should be based on the patient’s primary sleep disorder complaint. For example, a newer short-acting benzodiazepine with quick onset of action may be preferred in a patient whose primary problem is getting to sleep. Older anticonvulsants such as carbamazepine and valproic acid may be efficacious, but lack substantial study in RLS patients.\textsuperscript{156} Newer agents such as pregabalin and topiramate have also been studied with favorable preliminary results.\textsuperscript{156,165}

In addition to a dopamine agonist, nonpharmacologic therapies and behavioral techniques should also be recommended for J.J. Most important among these include discontinuing all RLS aggravators and practicing good sleep hygiene. Physical and mental activity (e.g., reading, playing card games, or working on the computer) if patients are unable to sleep can reduce symptoms.\textsuperscript{149} Counter stimuli such as massage or hot baths may be helpful.\textsuperscript{149}

\textbf{CASE 57-5, QUESTION 4:} After carefully considering the costs of therapy, J.J. and her physician choose levodopa to treat her RLS. She initially responds well to the therapy. One year later, J.J. returns for follow-up. Her dose of carbidopa/levodopa has progressively increased to three 25/100 mg tablets at bedtime. She describes continued worsening of her symptoms, and they do not seem to be relieved with increasing doses of carbidopa/levodopa. How should J.J.’s therapy be further adjusted?

J.J. is likely experiencing augmentation, a common problem with long-term use of dopaminergic drugs, particularly levodopa.\textsuperscript{166} Augmentation is described as a progressive worsening of RLS symptoms after an initial improvement, and is
manifested by gradually intensified symptoms that occur earlier in the evening and spread to other parts of the body. It is the most common side effect occurring with long-term use (>3 months) of dopaminergic agents, and usually occurs 6 to 18 months after therapy is initiated. Doses of dopaminergic agents are often increased in response, however, with each incremental dose increase symptoms progress more rapidly until they may occur continuously throughout the day. Although augmentation has been clinically recognized for many years, it has not been systematically studied. The exact etiology is uncertain, but it likely relates to the finding that RLS, unlike PD, is actually a hyperdopaminergic condition with an apparent postsynaptic desensitization that overcompensates during the circadian low point of dopaminergic activity in the evening and night. Adding dopaminergic in the evening initially corrects the symptoms, but ultimately leads to increasing postsynaptic desensitization.

The highest risk for augmentation is with levodopa. An estimated 30% to 45% of patients on levodopa will develop augmentation, compared with only 20% to 30% with dopamine agonists. The primary treatment strategy in dealing with augmentation is to withdraw the dopaminergic agent and substitute another nondopaminergic agent. Given her presentation, J.J. should have her carbidopa/levodopa discontinued. She should be counseled that her symptoms will likely rebound severely for 48 to 72 hours, but approximately 4 to 7 days later her symptoms should gradually return to baseline or pretreatment state.

With the discontinuation of carbidopa/levodopa in J.J., an alternative therapy should be selected. The selection of an alternative agent in cases in which the initial therapy failed or augmentation occurs must be approached on an individual basis. Although a number of agents are available to choose from, clinical experience generally guides the decision as lack of comparative trials precludes development of any formal recommendations. Because J.J. describes increasing pain with her RLS, it would be appropriate to initiate a trial of gabapentin. If gabapentin is ineffective or not tolerated, J.J. could be prescribed an opioid, which is also an acceptable choice in patients with RLS who have neuropathy or painful dysesthesias. Hydrocodone, oxycodone, methadone, codeine, and tramadol have all demonstrated efficacy in RLS. Augmentation does not prevent a future reintroduction of dopaminergic therapy; in J.J.’s case, a dopamine agonist could be added after an extended dopaminergic-free period if her symptoms are not completely controlled on gabapentin.

ESSENTIAL TREMOR

Clinical Presentation

**CASE 526**

**QUESTION 1:** K.H. is a 52-year-old white female office manager who was referred to a neurologist for evaluation of bilateral tremor. She is otherwise healthy and reports not taking any regularly prescribed medications. She describes her tremor as being present mainly when she performs voluntary movements. The tremor is not noticeable during rest. She also notices the tremor seems to disappear in the evening after drinking a couple of glasses of wine. The tremor interferes with several of her ADLs, including writing, eating, drinking from a cup, and inserting her keys into the ignition. She reports mild interference with her job function and some social embarrassment. No bradykinesia or rigidity is elicited on physical examination. A handwriting sample reveals large characters that are difficult to decipher. Family history reveals that her maternal grandmother and mother both had similar symptoms. What signs and symptoms are consistent with essential tremor in K.H.7?

Beginning in the mid-20th century, the term **essential tremor** (ET) has been consistently used to describe a kinetic tremor for which no definite cause has been established. ET is a common neurologic disorder with an estimated incidence of 0.16 cases per 100,000 person-years, and a prevalence of about 0.9% to 4.6%. Despite its commonness, it is underrecognized and undertreated, likely because it has been traditionally viewed as a monosymptomatic disorder of little consequence; more recently, it is recognized to be complex and progressive, resulting in significant disability in ADLs and job performance, and social embarrassment. Both the incidence and prevalence of ET increase with age. In addition, ethnicity and family history of ET are consistently identified risk factors; it is approximately five times more common in whites than blacks, and approximately 50% of patients report a positive family history. The latter finding suggests that genetic predisposition may play a role in ET; however, differences in inframural onset and severity suggest environmental factors may also influence underlying susceptibility to the disease. Several environmental toxins have been proposed as causes of ET, including β-carboline alkaloids (e.g., harmine and harmine) and lead, both of which have been found in elevated concentrations in patients with ET compared with normal control subjects.

Because parkinsonian tremor and ET are the most common forms of tremor observed in practice, it is important to distinguish between the two because the treatments differ substantially. Diagnostic criteria for ET developed by the Movement Disorder Society are summarized in Table 57-8. Tremor should first be identified as either an action or resting tremor. Action tremors include kinetic, postural, and isometric tremors. The defining feature of ET is a bilateral, largely symmetrical, 5- to 10-Hz kinetic tremor of the arms. The tremor can also affect head and postural tremor of the arms. The tremor can also affect head and voice. Kinetic tremor can be elicited in patients during voluntary movement, such as finger-to-nose test, signing their name, drawing spirals, or drinking water from a cup. Postural tremor occurs during sustained arm extension. Although both types of action tremors (kinetic or postural) can be present in ET and PD,
the presence of resting tremor is much more common in PD. Lack of resting tremor and absence of bradykinesia or rigidity in K.H., suggest the tremor is not parkinsonian. She describes interference of her tremor occurring with voluntary movement, such as in her ADLs and drinking from a cup. Other signs and symptoms that support a diagnosis of ET include her age, family history, large and tremulous handwriting (as opposed to micrographia in PD), and improvement in tremor with alcohol consumption. 

Table 57.9 summarizes the similarities and differences of ET and parkinsonian tremor.

Several medications and substances are known to cause tremors. All patients with tremor should have thorough medication history to rule out these possible causes. Medications commonly implicated include corticosteroids, metoclopramide, valproate, sympathomimetics (e.g., albuterol, amphetamines, pseudoephedrine), NBHA, tricyclic antidepressants, theophylline, and thyroid preparations. In addition, caffeine, tobacco, and chronic alcohol use can cause tremor that resembles ET. K.H. does not report taking any regularly prescribed medications, however, she should be questioned regarding any over-the-counter medication use as well as her caffeine and smoking habits, and alcohol use if applicable. 

The diagnosis of ET is based solely on clinical examination and neurological history. Neuromaging is not useful, and there are no available biological markers or diagnostic tests that are specific to ET. The evaluation of K.H.’s tremor should include laboratory analysis to rule out possible medical conditions associated with tremor. If clinical signs suggest the possibility of hyperthyroidism, thyroid function tests should be performed. In patients younger than 40 years of age who present with action tremor, serum ceruloplasmin can be tested to evaluate for possible Wilson disease.

**Treatment**

**CASE 57.6. QUESTION 2: What therapies are effective in treating ET? How should K.H. be treated?**

Patients with ET who have mild disability that does not cause functional disability or social embarrassment can go without treatment. Because K.H. is experiencing tremor that is interfering with her occupation and causing social embarrassment, she should be considered for pharmacotherapy (Table 57.10). It is important to note that although effective treatments exist, tremor is rarely eliminated completely. Factors predicting lack of response have not been readily identified.

Propranolol, a nonselective β-adrenergic receptor blocker, or primidone, an anticonvulsant, are recommended as first-line agents to treat ET. Propranolol is typically effective in doses of at least 120 mg/day, with about 50% of patients having long-lasting benefit. Long-acting propranolol is as effective as the regular-release formulation. Other β₁-selective blockers such as atenolol and metoprolol have also been studied, but with mixed findings. Propranolol has demonstrated greater efficacy than these β₁-selective agents, suggesting that blockade of β₂ receptors is of importance. β-Adrenergic receptor blockers with intrinsic sympathomimetic activity, such as pindolol, appear ineffective in ET. Caution should be exercised with propranolol in patients with asthma, congestive heart failure, diabetes mellitus, and antiventricular block.

Several studies have compared propranolol and primidone in ET, and they are considered to have similar efficacy. Primidone is metabolized to a phenobarbital-based metabolite; however, phenobarbital is inferior to primidone in treating ET. Acute adverse effects of primidone include nausea, vomiting, and ataxia, which can occur in up to one-fourth of patients, often limiting its use. The long-term tolerability of primidone is very good, however, and may actually be superior to propranolol. Primidone should be initiated at 12.5 mg/day and administered at bedtime to reduce the occurrence of acute side effects. It can be titrated gradually as tolerated up to 750 mg/day in divided doses, although side effects become more common at doses greater than 500 mg/day.

Other agents that have demonstrated variable efficacy in ET include gabapentin, pregabalin, topiramate, zonisamide, levetiracetam, and benzodiazepines (specifically, alprazolam and clonazepam). They are generally considered to be less-proven, second-line therapies, however. Adverse effects and potential for abuse (specifically with benzodiazepines) should be considered when an agent is selected. If oral pharmacotherapy options for ET are not beneficial, intramuscular injections of botulinum toxin A or surgical treatments can be used in selected patients. Targeted botulinum toxin A injections can reduce hand, head, and voice tremor; however, they are associated with focal weakness of the adjacent

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Essential Tremor</th>
<th>Parkinson Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kinetic tremor in arms, hands, or head</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Hemibody (arm and leg) tremor</td>
<td>0</td>
<td>++</td>
</tr>
<tr>
<td>Kinetic tremor &gt; resting tremor</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Resting tremor &gt; kinetic tremor</td>
<td>0</td>
<td>++</td>
</tr>
<tr>
<td>Rigidity or bradykinesia</td>
<td>0</td>
<td>++</td>
</tr>
<tr>
<td>Posural instability</td>
<td>0</td>
<td>++</td>
</tr>
<tr>
<td>Unal age of onset (years)</td>
<td>15-25, 45-55</td>
<td>55-65</td>
</tr>
<tr>
<td>Symmetry</td>
<td>Bilateral</td>
<td>Unilateral &gt; Bilateral</td>
</tr>
<tr>
<td>Family history of tremor</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Response to alcohol</td>
<td>+</td>
<td>0</td>
</tr>
<tr>
<td>Response to anticholinergics</td>
<td>0</td>
<td>++</td>
</tr>
<tr>
<td>Response to levodopa</td>
<td>0</td>
<td>+++</td>
</tr>
<tr>
<td>Response to primidone</td>
<td>+++</td>
<td>0</td>
</tr>
<tr>
<td>Response to propranolol</td>
<td>+++</td>
<td>+</td>
</tr>
</tbody>
</table>

**Handwriting analysis**

| Large, tremulous script        | Micrographia     |

** TABLE 57.9**

**Differentiation of Essential Tremor and Parkinson Disease**
Injections in the wrist can cause hand weakness, and 2010; 2005; 353:1021. 

Neurology.


10.875in Top: 0.373in Gutter: 0.664in

2002; 58:11. (24)

Neurology.

Neurology.

2006; 66:968. (7)

Greater improvement in self-reported 

September 17, 2011 2:31

LWBK915-57 LWW-KodaKimble-educational

P1: Trim: 8.375in 

A full list of references for this chapter can be found at 

thepoint.lww.com/AT10e

KEY REFERENCES AND WEBSITES

A full list of references for this chapter can be found at http://

thepoint.lww.com/AT10e. Below are the key references for this 

chapter, with the corresponding reference number in this chapter 

found in parentheses after the reference.

Table 57-10

Pharmacotherapy for Essential Tremor

Drug Initial Dose Usual Therapeutic Dose Adverse Effects

β-Blockers

Propranolol 10 mg every day to BID 140–320 mg divided every day to BID Bradycardia, fatigue, hypotension, depression, exercise intolerance

Atenolol 12.5–25 mg every day 50–150 mg every day Bradycardia, fatigue, hypotension, exercise intolerance

Nadolol 40 mg every day 120–240 mg every day Bradycardia, fatigue, hypotension, exercise intolerance

Anticonvulsants

Primidone 12.5 mg every day 50–750 mg divided every day to TID Sedation, fatigue, nausea, vomiting, ataxia, dizziness, confusion, vertigo

Gabapentin 100 mg every day 1,200–3,600 mg divided TID Nausea, drowsiness, dizziness, unsteadiness

Topiramate 25 mg every day 200–400 mg divided BID Appetite suppression, weight loss, paraesthesia, concentration difficulties

Pregabalin 75 mg BID 75–300 mg divided BID Weight gain, dizziness, drowsiness

Benzodiazepines

Alprazolam 0.125 mg every day 0.75–3 mg divided every day to BID Sedation, fatigue, potential for abuse

Clonazepam 0.25 mg every day 0.5–6 mg divided every day to BID Sedation, fatigue, ataxia, dizziness, impaired cognition

Miscellaneous

Botulinum toxin A Varies by injection site: 50–100 units/ arm for hand tremor; 40–400 units/neck for head tremor; 0.6–15 units/vocal cords for voice tremor; retreat no sooner than every 3 months (extend as long as possible) Hand weakness (with wrist injection); dysphagia, hoarseness, breathiness (with neck or vocal cord injection)

BID, two times daily; TID, three times daily.

area. Injections in the wrist can cause hand weakness, and dysphagia, hoarseness, and breathlessness can occur with injections into the neck or vocal cords. The use of botulinum toxin injections in the United States is also limited by cost. Treatment should occur with the lowest dose, and the interval should be as long as possible between injections. DBS of the ventral intermediate nucleus of the thalamus or unilateral thalamotomy is highly efficacious in reducing ET. Greater improvement in self-reported measures of function and fewer adverse events make DBS the preferred surgical option of the two. K.H. is otherwise healthy; she is a good candidate for propranolol therapy. Propranolol can be initiated as needed or on a scheduled basis depending on the degree of impairment and desire of the patient. If the decision is made with K.H. to use propranolol on an as-needed basis, she should begin with one-half of a 20-mg tablet administered 30 minutes to 1 hour before the desired effect. The dose can be increased from one-half to two tablets. An example of a situation in which this may occur is if she wants to avoid embarrassment with attending a function or before certain tasks requiring manual dexterity at work. Given the degree of her impairment, she is probably a better candidate for chronic suppressive therapy with propranolol. In this situation, she can be prescribed 10 mg twice daily and titrated every few days up to 120 to 360 mg/day in divided doses.

Key References

Parkinson Disease


Suchowersky O et al. Practice parameter: neuroprotective strategies and alternative therapies for Parkinson disease (an evidence-based overview): report of the Quality Standards Subcommittee