Recognizing the Early Signs of Parkinson Disease and Optimizing Patient Outcomes

Introduction
Parkinson disease (PD) is the second most common neurodegenerative disorder after Alzheimer disease. Approximately 1 million people in the United States have PD, and 50,000 to 60,000 new cases are diagnosed annually. Although characterized by motor symptoms, specifically tremor, rigidity, bradykinesia, and postural instability, PD has an insidious onset. Nonmotor symptoms may appear a decade or more before the onset of motor symptoms and are often present long before a definitive diagnosis of PD is made. Recognizing nonmotor symptoms and early motor symptoms can enable pharmacists to collaborate effectively with physicians to intervene sooner and help maintain patients’ quality of life.

Pathophysiology
PD is caused by the deterioration or loss of dopamine-producing neurons in the brain. This damage and consequent cell death occur in the substantia nigra region for an estimated 6 years before any motor symptoms develop. In other areas of the brain, such as the medulla oblongata and pontine tegmentum, this damage is believed to occur even before the substantia nigra is affected. By the time motor symptoms appear, approximately 70% to 80% of dopaminergic neurons have already been lost.

PD tends to be a disease of older people (>65 years of age), and rarely occurs before 40 years of age. Symptoms of early PD are often nonspecific and frequently attributed to “aging.” Over time, people lose dopaminergic neurons in the substantia nigra, but in individuals with PD, this process is accelerated.

Early Nonmotor Symptoms of PD
The most common early nonmotor symptoms of PD are constipation, rapid eye movement sleep behavior disorder (RBD), olfactory impairment, and cardiac sympathetic denervation. RBD is characterized by the unconscious acting out of dreams. About half of patients with RBD develop PD. Constipation (<1 bowel movement daily) is associated with a nearly threefold increase in risk of PD in men. Cardiac sympathetic denervation probably occurs in most if not all patients with PD. This condition is defined as a loss of functional cardiac sympathetic nerve terminals, represented by abnormal blood pressure response to the Valsalva maneuver. It also can be referred to as long QT syndrome. Olfactory impairment (altered sense of smell) is a common early symptom that distinguishes PD from other parkinsonian syndromes.

Pharmacists may be able to recognize early PD by being aware of the medications patients are using or complaints they have related to early nonmotor symptoms of PD. For instance, a patient may purchase several over-the-counter (OTC) remedies for constipation or have concerns about an altered sense of smell. A patient with cardiac sympathetic denervation may have episodic or persistent orthostatic hypotension, which pharmacists can recognize from complaints of fatigue, lightheadedness, and dizziness, particularly if these symptoms occur when the patient arises from a seated or supine position. These scenarios present pharmacists with opportunities to question patients about other nonmotor symptoms that may be early manifestations of PD.

Cardinal Motor Signs and Other Symptoms of PD
Tremor, rigidity, bradykinesia, and postural instability are the four cardinal signs of PD; however, patients may have PD for years or even decades before the signs develop. These and other motor symptoms of PD are typically unilateral at onset, but usually become asymmetrically bilateral with disease progression. Tremor in PD commonly is more prominent when a patient is still or at rest. Rigidity is nearly universal in people with PD. A patient with rigidity may complain of muscle pain or soreness. Bradykinesia is a slowness of movement. Postural instability causes
problems with balance and increases the incidence of falls and therefore fractures. Pharmacists should advise such patients to have their bone health evaluated and provide counseling about calcium and vitamin D intake and other strategies to improve bone health and reduce fracture risk. Other symptoms seen in the early motor phases of PD include:

- Difficulty arising from a chair or turning in bed
- Masked facies (loss of facial expression due to muscle rigidity)
- Micrographia (small cramped handwriting)
- Hypophonia (low or muffled speech)
- Decreased arm swing on the affected side when walking
- Stooped shuffling gait
- “Freezing” (inability to move when attempting to walk)
- Painful foot cramps
- Additional nonmotor symptoms that are sometimes present both in early and later stages of PD include cognitive slowing, depression, anxiety, double vision, and salivation.

**Differential Diagnosis**

Idiopathic PD must be differentiated from drug-induced PD, because the latter usually can be reversed by discontinuing the offending medication. A careful and complete medication history is necessary to determine whether a particular drug is contributing to the development of PD. Table 1 lists drugs that commonly cause drug-induced

<table>
<thead>
<tr>
<th>Drugs that Commonly Cause Drug-Induced Parkinson's Disease</th>
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**LEARNING OBJECTIVES**

At the completion of this activity, the pharmacist will be able to:

- Describe advances in the understanding of the pathophysiology and pathology of PD.
- Analyze the importance of early diagnosis and management of PD.
- Identify early nonmotor symptoms of PD.
- Differentiate the mechanisms of action for symptomatic therapies available to treat early PD and describe potential neuroprotective mechanisms of action for existing and emerging therapies.
- Evaluate current clinical trials of neuroprotective or disease-modifying effects of PD therapies.
- Formulate options for helping patients maximize their quality of life by managing PD symptoms and adverse effects of PD medications.

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**SUPPORT**

This activity is supported by an independent educational grant from Teva Neuroscience.

**DISCLOSURES**

Melody Ryan, PharmD, MPH, declares no conflicts of interest or financial interests in any product or service mentioned in this activity, including grants, employment, gifts, stock holdings, and honoraria.

Stephen M. Setter, PharmD, DVM, CDE, CGP, FASCP, has received honoraria for serving on the speakers bureau for Teva and has received research grant support from Teva.

APhA’s editorial staff declares no conflicts of interest or financial interests in any product or service mentioned in this activity, including grants, employment, gifts, stock holdings, and honoraria.

This publication was prepared by Lauren Cerruto and Amanda Bach of MedPen, Inc., on behalf of the American Pharmacists Association.
PD but note that most patients can take these drugs without developing PD-like symptoms.

**Table 1. Common Offenders in Drug-Induced Parkinson Disease**

<table>
<thead>
<tr>
<th>Antipsychotics</th>
<th>Dopamine Depletors</th>
<th>Gastrointestinal Agents</th>
<th>Dopamine Agonists</th>
<th>Drug Combinations</th>
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<tbody>
<tr>
<td>Haloperidol</td>
<td>Alpha-methyl-dopa</td>
<td>Metoclopramide</td>
<td>Reserpine</td>
<td>Amitriptyline/perphenazine</td>
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<td>Chlorpromazine</td>
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<td>Thoridazine</td>
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<td>Risperdone</td>
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<td>Olanzapine</td>
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Source: References 18–20.

**Current PD Therapies: Management of Early Motor Symptoms**

Traditionally, both diagnosis and treatment for PD were delayed until the onset of bothersome motor symptoms. Clinicians’ increasing ability to recognize PD at earlier stages raises the question of whether PD therapy should be started as early as possible or delayed until needed for relief of motor symptoms. Early initiation of therapy as soon as symptoms begin to interfere with daily activities has the advantage of maximizing function, and theoretically may preserve basal ganglia compensatory mechanisms. The decision on when to initiate therapy should be individualized based on the patient’s need for symptomatic relief as well as the therapy’s potential for disease modification (discussed in the next section), short- and long-term tolerability, risk of drug interactions, and cost. Early treatment typically consists of carbidopa/levodopa, a dopamine agonist, or a monoamine oxidase type B (MAO-B) inhibitor; other available options for initial monotherapy include amantadine or an anticholinergic agent.

There are few studies on the effect of PD therapies on specific nonmotor symptoms, although behavior, mood, activities of daily living, and symptoms such as salivation and speech are assessed in the PD rating scales used to study many of these medications. There is some evidence that PD therapies may help reduce depression. On the other hand, levodopa, dopamine agonists, and anticholinergic agents may exacerbate hallucinations/dementia, and anticholinergic agents may exacerbate constipation and cognitive problems.

**Carbidopa/Levodopa**

Most PD therapies work by countering the dopamine deficiency associated with PD. Dopamine itself does not cross the blood-brain barrier and cannot be directly administered as a PD therapy. Levodopa is an inactive dopamine precursor that is converted to dopamine. To prevent peripheral metabolism of levodopa, it is given with a decarboxylase inhibitor (carbidopa, in the United States) that does not cross the blood-brain barrier. With the addition of carbidopa, the levodopa dose can be decreased by 75% and titrated more rapidly, and there are fewer gastrointestinal adverse effects.

Available formulations of carbidopa/levodopa in the United States include oral tablets, sustained-release tablets, and orally disintegrating tablets (ODTs); a liquid formulation can be compounded by adding water and ascorbic acid to the drug. Standard oral and ODT formulations are typically administered three to four times daily, but are sometimes given more frequently (up to every 2 hours). The sustained-release formulation is administered two to four times per day.

Carbidopa/levodopa remains the most effective therapy for control of nearly all classic PD motor symptoms. Carbidopa/levodopa is less likely to alleviate freezing episodes, postural instability, autonomic symptoms, mood disturbances, pain, sensory symptoms, or dementia. Most patients with PD use carbidopa/levodopa at some point during the course of their disease.

With long-term use, carbidopa/levodopa may cause adverse motor effects in some patients, especially those with young onset of PD and those using higher levodopa doses. These adverse effects include dyskinesia (involuntary movements), early wearing off at the end of the dosing cycle, and “on-off” fluctuations in which the patient shifts between good mobility and motor dysfunction.
bloodstream and the brain, attributable to levodopa’s short half-life, may account for these motor fluctuations.\textsuperscript{24} Fluctuations can be diminished by using sustained-release carbidopa/levodopa or adding a catechol-O-methyltransferase (COMT) inhibitor (e.g., entacapone) or an MAO-B inhibitor. Dyskinesias can be reduced by slightly decreasing the levodopa dose.\textsuperscript{22} To obtain the right balance, patients can make small temporary adjustments in their carbidopa/levodopa dose depending on the activities they have planned for the day. For example, they may need a little more medication for a day full of activities or a little less for a day spent sitting in a car for a long ride.

Because of the risk of motor complications, many clinicians prefer to reserve carbidopa/levodopa for patients who have moderate to severe symptoms, and to use alternate therapies for early management of PD, while it is still mild. The decision to use carbidopa/levodopa should be individualized because some patients with bothersome motor symptoms would rather tolerate the dyskinesias in order to have better mobility than to have less control of PD motor symptoms.

**Dopamine Agonists**

Dopamine agonists directly stimulate dopamine receptors.\textsuperscript{24} The older ergot-derived dopamine agonists bromocriptine and pergolide were associated with significant adverse effects including heart-valve abnormalities. Pergolide has been removed from the market; bromocriptine remains available but is rarely used. Newer nonergot-derived oral dopamine agonists (i.e., pramipexole and ropinirole) have not been associated with these adverse effects and are used as initial monotherapy or adjuncts to levodopa\textsuperscript{24} or (off-label) as adjuncts to MAO-B inhibitors. Pramipexole and ropinirole are each available in standard oral formulations, for administration three times daily,\textsuperscript{25,26} and in extended-release formulations, for once daily administration.\textsuperscript{27,28} In more advanced PD, apomorphine, an injectable dopamine agonist, is used as a “rescue” therapy for treating severe “off” episodes, and must be taken with antiemetic medications to reduce significant nausea.\textsuperscript{24} A transdermal dopamine agonist, rotigotine, was approved by the U.S. Food and Drug Administration (FDA); however, it has been temporarily withdrawn from the market because of crystal formation in the patches. A new formulation is now being developed.\textsuperscript{29}

Dopamine agonists provide good control of motor symptoms, may delay motor complications and the need to initiate carbidopa/levodopa, and allow a lower dose of carbidopa/levodopa to be used.\textsuperscript{22,30} A meta-analysis of 29 clinical trials found that PD symptom control (based on clinician-rated disability scales) was not as good with dopamine agonists as with carbidopa/levodopa.\textsuperscript{31} Dopamine agonists were less likely to cause dyskinesias, dystonias, or motor fluctuations but more likely to cause nonmotor adverse effects (e.g., edema, somnolence, constipation, dizziness, psychosis, nausea) compared with carbidopa/levodopa.\textsuperscript{31}

**MAO-B Inhibitors**

Another strategy to address dopamine depletion in PD is to keep available dopamine around longer. Monoamine oxidase (MAO) is one of the enzymes responsible for breaking down dopamine. Therapies that block MAO slow dopamine’s metabolism, leaving more dopamine available in the brain.\textsuperscript{24} Selective MAO-B inhibitors provide another therapeutic option for patients with mild motor disability and early PD.\textsuperscript{22,30} Rasagiline is an FDA-approved MAO-B inhibitor for use as initial monotherapy,\textsuperscript{32} and selegiline is commonly used off-label for this indication.\textsuperscript{22} Both are also approved as adjuncts to levodopa. Rasagiline standard oral tablets are administered once daily.\textsuperscript{32} Selegiline is available in a standard oral formulation with once-or twice-daily administration\textsuperscript{33} and an OD formulation given once daily.\textsuperscript{34} A transdermal selegiline formulation is available for treatment of depression\textsuperscript{35}, however, it is not approved for treatment of PD.

Selegiline proved superior to placebo in a randomized trial,\textsuperscript{36} but it is largely perceived to offer weaker symptomatic benefits compared with levodopa or dopamine agonists—a perception supported by a meta-analysis of two studies comparing selegeline with dopamine agonists and levodopa.\textsuperscript{37} Rasagiline’s use as initial monotherapy is supported by results from the Rasagiline Mesylate in Early Monotherapy for Parkinson’s Disease Outpatients (TEMPO)\textsuperscript{38} and

**Anticholinergic Agents**

Dopamine deficiency in PD appears to disturb the balance between acetylcholine and dopamine neurotransmissions in the basal ganglia.\textsuperscript{22} Although acetylcholine levels are not technically elevated in PD, reducing these levels restores the dopamine-acetylcholine balance. Anticholinergic agents (e.g., trihexyphenidyl, benzotropine) are therefore sometimes used, particularly in younger patients (<60 years of age) whose predominant PD symptom is resting tremor. They are less effective for controlling other PD symptoms.\textsuperscript{22} Anticholinergic agents are administered two to three times daily.\textsuperscript{24} Anecdotally, some patients take them only as needed, such as in social situations during which tremor is particularly bothersome.

**Amantadine**

Amantadine was first developed as a treatment for influenza but was serendipitously discovered to have activity in PD.\textsuperscript{24} Its mechanism of action may include stimulation of dopamine release or dopamine receptors, blockade of dopamine reuptake, and possibly anticholinergic activity.\textsuperscript{22} Amantadine is used as initial monotherapy for newly diagnosed patients with mild PD symptoms. Its beneficial effect...
tends to diminish after a few weeks to months.\textsuperscript{24} Amantadine is available in capsules and oral suspension, administered two to three times daily.\textsuperscript{24}

**Treatment of Early PD: Potential for Neuroprotection?**

In the earliest stages of PD, treatment is sometimes considered for the purpose of disease modification—that is, to slow the progression of PD. No therapy has been unequivocally shown to prevent loss of dopaminergic neurons, and even clinical disease modification continues to be debated. Studies of neuroprotection have relied on surrogate biomarkers, including neuroimaging of the nigrostriatal system, and on modified clinical trial designs such as posttreatment washout periods or delayed-start designs (Figure 1).

In a posttreatment washout study, it is assumed that any residual benefit seen during the washout period would be attributable to neuroprotection; however, there is much debate regarding the duration of the washout period required to assess such effects. Delayed-start designs compare early versus later initiation of treatment. A disease-modifying therapy would be expected to show a sustained advantage with early treatment initiation even after all participants were receiving therapy in the later phase.

Clinical trials to assess neuroprotection of ropinirole and pramipexole have used neuroimaging—such as \textsuperscript{18}F-dopa positron emission tomography (FD-PET) or \textsuperscript{2}β-carboxymethoxy-3β(4-iодophенил)tropane (β-CIT) uptake on single-photon emission computed tomography (SPECT)—as a biomarker of dopaminergic activity in the nigrostriatum.\textsuperscript{44,45} These neuroimaging trials suggest that loss of function (and presumably loss of dopaminergic neurons) in this area of the brain is slower in patients taking dopamine agonists compared with levodopa, despite the ability of levodopa to provide greater symptomatic relief.\textsuperscript{44,45} In contrast to the neuroimaging data, however, results of a delayed-start trial of pramipexole did not show a disease-modifying effect.\textsuperscript{46}

MAO-B inhibitors, particularly rasagiline, hold promise as potential disease-modifying agents. Two delayed-start trials (TEMPO and ADAGIO) evaluated the disease-modifying potential of rasagiline.\textsuperscript{38,39} In both studies, rasagiline, at its approved dose of 1 mg/d, had a greater impact on disability when started earlier than it did after a 6- to 9-month delay.\textsuperscript{38,39} (Disability was measured with the UPDRS.) This finding suggests that rasagiline may have more than symptomatic benefit: it also may modify the course of the disease. However, only the TEMPO trial confirmed similar benefit with a higher off-label dose of rasagiline 2 mg/d.\textsuperscript{38} The ADAGIO study required that three end points all be met to satisfy a positive result: (1) superiority to placebo in the rate of change of UPDRS scores between weeks 12 and 36, (2) superiority to delayed-start treatment in the change in UPDRS score between baseline and week 72, and (3) noninferiority to delayed-start treatment in the rate of change in UPDRS score between weeks 48 and 72.\textsuperscript{39} Rasagiline 1 mg/d met all three end points, demonstrating that patients who start treatment later do not “catch up” to those who start earlier. Rasagiline 2 mg/d met only the first and third end points,\textsuperscript{39} and thus did not meet the full criteria for disease modification. The investigators speculated that a greater symptomatic benefit with the higher dose may have masked its disease-modifying activity.\textsuperscript{39}

The Deprenyl [Selegiline] and Tocopherol Antioxidative Therapy of Parkinsonism (DATATOP) trial compared selegiline (10 mg/d) plus placebo, vitamin E (2000 IU/d) plus placebo, selegiline plus vitamin E at these same doses, and double placebo in 800 patients with early PD.\textsuperscript{36,47} There was no benefit to vitamin E, but use of selegiline slowed progression of disability, significantly delaying the time until levodopa was needed by an average of almost 9 months.\textsuperscript{36} Initially, this result was attributed at least in part to a neuroprotective effect, because symptomatic benefits of selegiline were thought to be modest,\textsuperscript{37} and even patients who initially had no improvement in total UPDRS scores on treatment still showed a delay in time until need for levodopa.\textsuperscript{36}

After the benefit of selegiline was established, the DATATOP protocol

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**Figure 1. Drug Trial Designs to Evaluate Neuroprotection**

<table>
<thead>
<tr>
<th>Washout Study Design</th>
<th>Delayed-Start Study Design</th>
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<tr>
<td><strong>Symptomatic Only</strong></td>
<td><strong>Symptomatic Only</strong></td>
</tr>
<tr>
<td>Start Drug therapy</td>
<td>Early start Delayed start</td>
</tr>
<tr>
<td>0% Disability</td>
<td>0% Disability</td>
</tr>
<tr>
<td><strong>Neuroprotective Only</strong></td>
<td><strong>Neuroprotective Only</strong></td>
</tr>
<tr>
<td>End Drug therapy</td>
<td>Early start Delayed start</td>
</tr>
<tr>
<td>100% Disability</td>
<td>100% Disability</td>
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Graphics courtesy of Melody Ryan, PharmD, MPH.
was modified to withdraw treatment, and patients were reassessed after a 2-month washout. Patients treated with selegiline experienced mild but significant worsening in the motor score of the UPDRS at 1 and 2 months compared with patients who had not received selegiline. After that phase of the trial, all DATATOP participants were offered open-label selegiline therapy, tantamount to a delayed-start design. Among the subgroup of patients not yet taking levodopa, those who had received selegiline since the start of the trial (the “early-start group”) had no sustained advantage over those who started selegiline during the later open-label phase (the “delayed-start group”). Among the subgroup of patients who were taking levodopa during the open-label phase, earlier initiation of selegiline did not reduce motor complications (wearing off, dyskinesias, on-off episodes, freezing) compared with later initiation of selegiline. Thus, later data from DATATOP do not show evidence of disease modification; however, continued use of selegiline may nonetheless provide clinical benefit. Some of the patients taking levodopa and selegiline were rerandomized to either continue selegiline or switch to placebo. Continued selegiline for up to 7 years slowed the rate of motor decline and reduced the risk of freezing but increased the risk of dyskinesias compared with discontinuation of selegiline.

Questions have been raised regarding whether levodopa damages rather than preserves dopaminergic neurons. This question was considered in the Earlier Versus Later Levodopa (ELLDOPA) study, which compared carbidopa/levodopa (12.5/50 mg, 25/100 mg, or 50/200 mg administered three times daily) with placebo and concluded with a 2-week washout period. During treatment, levodopa provided a clear symptomatic effect (Figure 2). During the washout, UPDRS scores worsened in the levodopa group, but did not reach the placebo group’s level. These clinical findings contradict the hypothesis of levodopa being neurotoxic; however, neuroimaging data showed that the levodopa groups had a faster rate of decline in β-CIT uptake on SPECT. The imaging data may signify greater degeneration of dopaminergic neurons in the levodopa group. It is not clear how to reconcile the discrepancy between the clinical findings and imaging data.

Patients with PD often take alternative therapies such as vitamins C and E, coenzyme Q₁₀, or creatine because they have heard that these therapies can be beneficial in PD. As shown in the DATATOP trial, vitamin E does not alter the course of PD. Similarly, a randomized, prospective, phase II trial of coenzyme Q₁₀ found it safe and well tolerated, but did not find significant effects on disability compared with placebo in patients with midstage PD. Coenzyme Q₁₀ is currently being assessed in a placebo-controlled phase III trial. Vitamin C is a weak COMT inhibitor, and in a six-patient study produced modest functional improvements; however, large-scale controlled trials have not been performed. Small studies suggest that vitamin C also may alter levodopa pharmacokinetics, increasing the area under the curve and peak drug concentration, while reducing the time to peak drug concentration. In an 18-month phase II pilot trial, neither creatine nor minocycline met the threshold for futility with regard to slowing progression of PD-related disability. Creatine is currently being assessed in a large-scale, placebo-controlled, phase III clinical trial.

### Additional Adverse Effects of PD Therapies

In addition to the risk of motor complications, PD therapies have a number of other adverse effects that require careful monitoring and management. Carbidopa/levodopa and dopamine agonists share dopaminergic adverse effects such as nausea, light-headedness/dizziness, somnolence, fatigue, constipation, sleep disturbances, confusion, and hallucinations. It is often difficult to determine whether some of these symptoms are PD related or drug induced. Orthostatic hypotension is a common adverse effect of many PD medications, even in patients who were previously hypertensive.

Dopamine agonists are more likely than carbidopa/levodopa to cause excessive daytime sleepiness, visual hallucinations, confusion, leg edema, and compulsive behaviors (e.g., excessive eating, shopping, gambling, or sexual urges). Leg edema is often mistaken for a sign of cardiac dysfunction. Dyskinesias may occur in patients taking dopamine agonists but are less common than with carbidopa/levodopa.
Adverse effects of rasagiline include flu-like symptoms, arthralgia, depression, dyspepsia, infection, and headache. Selegiline’s adverse effects include nausea, musculoskeletal injuries, non–life-threatening cardiac arrhythmias, and elevated serum amnoplus transferase levels. Unlike selegiline ODT and rasagiline, the standard oral formulation of selegiline is metabolized to amphetamine and methamphetamine. These amphetamine metabolites may give some patients the feeling of having an “energy” boost, which can be an advantage, but can also contribute to sleep abnormalities such as insomnia, jitteriness, and confusion. Many clinicians advocate dosing selegiline in the morning and early evening to avoid interference with sleep.

Amantadine can cause nausea, lightheadedness, insomnia, confusion, and hallucinations. Its neuropsychiatric adverse effects tend to limit its use in older patients and those with dementia. Rarely, amantadine causes livedo reticularis, a reversible mottling of the skin, usually on the legs, which does not necessarily require treatment discontinuation. Amantadine is cleared renally and the dose must be adjusted according to creatinine clearance if the patient has renal impairment.

Anticholinergic agents can cause memory impairment, confusion, hallucinations, sedation, dysphoria, dry mouth, blurred vision, and urinary retention. These agents are typically used in younger patients with PD, because older patients tend to tolerate the adverse effects poorly.

**Understanding Potential Food and Drug Interactions**

**MAO-B Inhibitors and “Cheese Reaction”**

A potentially fatal hypertensive crisis occurs when vasoactive dietary tyramine is allowed to reach the bloodstream. It has been dubbed the “cheese reaction” because aged cheese has among the highest tyramine levels of all foods. Tyramine is normally metabolized by MAO type A (MAO-A) before it reaches the circulation, so inhibition of MAO-A increases the risk of this adverse event. At recommended doses, both rasagiline and selegiline are selective for MAO-B and unlikely to cause the cheese reaction, therefore dietary restriction of tyramine is largely not required with these agents.

Nonetheless, patients taking MAO-B inhibitors may want to avoid foods that have a high tyramine content.

**MAO-B Inhibitors and Antidepressants**

Concurrent use of an MAO inhibitor with antidepressants or medications that affect serotonin levels can increase the risk of serotonin syndrome. The most serious reactions have occurred with therapies that inhibit MAO-A, including nonselective MAO inhibitors. Serotonin syndrome is very rare with selective MAO-B inhibitors and is listed as a warning or precaution in the product labeling but not as a contraindication. In clinical practice, MAO-B inhibitors and antidepressants are commonly used together. Pharmacists should discuss with the prescriber the risks and benefits of concomitant administration of MAO-B inhibitors and antidepressants for a specific patient. Use of meperidine, tramadol, methadone, propoxyphene, dextromethorphan, St. John’s wort, and other MAO inhibitors (selective or nonselective) concurrent with MAO-B inhibitors is contraindicated, however. See [www.pharmacoday.org/pdf/2010/CE_CE_Jul2010.pdf](http://www.pharmacoday.org/pdf/2010/CE_CE_Jul2010.pdf) for more information on serotonin syndrome in patients taking MAO-B inhibitors and antidepressants.

**PD Therapies and Cytochrome P450 Enzymes**

The hepatic enzyme cytochrome P450 (CYP) 1A2 metabolizes ropinirole and rasagiline. As a result, CYP1A2 inhibitors such as ciprofloxacin, fluvoxamine, and cimetidine may increase their plasma concentra-

**Prampixole and Renally Secreted Drugs**

Because pramipexole is excreted renally by cationic tubular secretion, its elimination is reduced by other drugs that either inhibit or compete for cationic tubular secretion; such drugs include cimetidine, verapamil, probenecid, ranitidine, diltiazem, quinine, and triamterene.

**Investigational Therapies for PD**

As shown in Table 2, a number of new therapies for PD are now in phase III clinical trials, although most of them are being developed as adjuvantive treatments for later-stage PD. In addition, a phase III placebo-controlled trial of embryonic dopamine cell implant surgery is ongoing.

**Maximizing Quality of Life by Managing Nonmotor Symptoms and Adverse Drug Effects**

Nonmotor symptoms and adverse effects of PD medications can have a tremendous impact on patients’ quality of life and should be addressed in encounters between pharmacists and patients.

**Orthostatic Hypotension**

Orthostatic hypotension is a common symptom of PD that can be exacerbated by dopaminergic medications. Signs of orthostatic hypotension include lightheadedness, fatigue, unsteadiness, headache, neck tightness, and cognitive slowing. The first step in managing orthostatic hypotension is to taper off antihypertensive drugs and other non-PD drugs if necessary. Treatment with fludrocortisone (0.1–0.4 mg/d) or midodrine (2.5–30 mg/d) may raise blood pressure, and intranasal desmopressin (5–40 μg at bedtime) may be used as an adjuvant to fludrocortisone as needed. Patients should be advised to increase salt intake (with their physician’s approval), avoid lying prone, wear waist-high stockings, increase fluid intake, move slowly.

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### What Do You Think?

Is it best to wait until a patient has particularly bothersome motor symptoms before initiating treatment for PD, or should therapy be initiated as early as possible? Take a moment to list possible pros and cons of early PD treatment:

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<th>Pros</th>
<th>Cons</th>
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See page 9 for answers.
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when rising or lifting the head, and monitor blood pressure at home.22,78

Constipation

Constipation, a common and often early symptom of PD, can be particularly bothersome to patients. Patients should be advised to increase fluid intake, dietary fiber, and exercise.22 If these measures are insufficient, patients can try OTC stool softeners22 or isosmotic macrogol (polyethylene glycol)77 under physician guidance. There are anecdotal reports of some patients benefitting from homemade natural laxatives that include blended prunes, raisins, figs, senna tea, sugar, and juice.

Bladder Dysfunction

Patients who frequently awaken to urinate may have to curtail fluid intake after the evening meal.22 Pharmacologic therapies used in the management of bladder dysfunction include peripherally acting anticholinergics such as oxybutynin (5–10 mg at bedtime or three times daily), propantheline (7.5–15 mg at bedtime or three times daily), or tolterodine tartrate (1–2 mg twice daily based on individual response and tolerability, or long-acting formulation at 4 mg/d).22 If these therapies are ineffective, hyoscymamine (0.15–0.30 mg at bedtime or on a four times daily schedule) may be considered.22 Patients with persistent bladder problems should be referred to a urologist.

Dysphagia

Patients with PD frequently have difficulty swallowing. Pharmacists can educate such patients to “lube the tube” by drinking to lubricate the esophagus before swallowing pills, or switch to ODT formulations if available.24 Drinking and eating may be facilitated by using a food-thickening product in liquids and pureeing foods.79 Scheduling meals during “on” times also can be helpful.22

Sialorrhea

Sialorrhea (drooling) can be socially embarrassing and can increase the risk of aspiration pneumonia or skin erosions.22 Strategies that may help prevent drooling include gum chewing, use of 1 to 2 drops of atropine ophthalmic solution placed under the tongue to dry out the mouth, oral anticholinergic agents, and botulinum toxin injections into the salivary gland.22,24

Nausea

Nausea is a potential adverse effect of most PD therapies. Nausea associated with carbidopa/levodopa may be alleviated by adding single-agent carbidopa23 or taking the dose with food.22,79 Other strategies for managing nausea include adding trihexyphenidyl to the drug regimen24 and advising patients to ingest ginger products (e.g., ginger ale, ginger tea, gingersnaps).79 The following medications should be avoided because they may cause PD-like symptoms: metoclopramide, phenothiazine, promethazine, perphenazine.18,24

Sleep Abnormalities and Excessive Daytime Sleepiness

Sleep abnormalities associated with PD include fragmented sleep (due to PD symptoms), RBD, periodic limb movements, restless legs syndrome, and sleep apnea.80 The complexities of sleep abnormalities require management by a neurologist or a sleep specialist to determine the best course of action for the individual patient. Anticholinergics such as diphenhydramine may facilitate sleep but can cause constipation or cognitive impairment.81 Clonazepam or melatonin is often used for RBD; however, data in patients with PD are lacking.77 Excessive daytime sleepiness may be a result of interrupted sleep due to sleep abnormalities but also may be associated with advanced age, advanced PD, or use of dopaminergic medication. This symptom may be transient or chronic. Patients who are excessively sleepy during the day should be advised to take short naps, consider increasing caffeine intake (if not contraindicated), and increase daytime stimulation. In addition, if sudden sleep episodes occur without warning, patients should stop driving79 and tell their physician. Sedating medications and the dose of dopamine agonists should be reduced.22 Modafinil offers modest benefits in promoting wakefulness.22

Psychosis and Dementia

Psychosis in patients with PD may include disorientation, hallucinations, and delusions. The first step is to simplify the patient’s medication regimen.22 Discontinue unnecessary non-PD medications.22 Gradually reduce the dose or discontinue PD medications—stopping levodopa last.24,79 If these steps are insufficient to reverse the psychosis, consider treatment with quetiapine or clozapine.79,82 Clozapine is preferred for treatment of hallucinations, but is associated with agranulocytosis, necessitating regular white blood cell count monitoring.83 Chlorpromazine, haloperidol, olanzapine, perphenazine, risperidone, and aripiprazole may worsen PD.22

### Table 2. Investigational Therapies in Phase III Trials for PD

<table>
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</tr>
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<tr>
<td>Pardoprunox&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Partial dopamine D&lt;sub&gt;2&lt;/sub&gt; receptor agonist and serotonin 5-HT&lt;sub&gt;1A&lt;/sub&gt; agonist</td>
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<tr>
<td>Developed for use in advanced PD</td>
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<tr>
<td>Lisuride</td>
<td>Ergotamine dopamine D&lt;sub&gt;2&lt;/sub&gt; receptor agonist and serotonin 5-HT&lt;sub&gt;2B&lt;/sub&gt; antagonist, given continuously via subcutaneous pump</td>
</tr>
<tr>
<td>Sumanirrole&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Highly selective dopamine D&lt;sub&gt;2&lt;/sub&gt; receptor agonist</td>
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<td>Carbidopa/levodopa administered continuously via pump to the duodenum</td>
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<sup>a</sup> IPX066 is also being investigated for conversion from regular carbidopa/levodopa or carbidopa/levodopa/entacapone in advanced PD.

<sup>b</sup> Pardoprunox is also being investigated as an adjunct to levodopa.

<sup>c</sup> Sumanirrole did not meet criteria for noninferiority to ropinirole as monotherapy in early PD.

MAO-B = monoamine oxidase type B; PD = Parkinson disease.

Source: References 62–75.

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MAO-B = monoamine oxidase type B; PD = Parkinson disease.

Source: References 62–75.
PD patients with dementia may benefit from rivastigmine, donepezil, or memantine.22

Depression
No antidepressant has been proven more effective than any other in patients with PD, so the decision of which drug to prescribe should be based on the preferences and response of the individual patient. Selective serotonin reuptake inhibitors are commonly used,23 but rasagiline clinical trials did not allow concomitant use of fluoxetine and fluvoxamine with rasagiline. Tricyclic antidepressants may be effective but may have anticholinergic adverse effects.22 If antidepressants are used concurrently with an MAO-B inhibitor, the patient should be monitored carefully for serotonin syndrome. Ask patients what they know about their depression and advise them to undergo counseling or join a support group, discuss their symptoms with their family and others they trust for support, and exercise regularly.

Pain
Pain in PD may result from limb rigidity, dystonia, or primary central pain. Treatment is dependent on the source of pain, which must first be identified. Medications that may be used include OTC analgesics, muscle relaxants, dopaminergic medications, and benzodiazepines.24

Conclusion
Nonmotor symptoms such as olfactory dysfunction, RBD, constipation, and cardiac sympathetic derervation are often the first manifestations of PD. Unfortunately, these symptoms are nonspecific, which complicates early diagnosis. There is ongoing controversy regarding whether treatment should be initiated for early PD—that is, PD diagnosed either before the onset of motor symptoms or at a stage when motor symptoms are mild and not particularly bothersome to the patient. Data on rasagiline is suggestive of a disease-modifying effect, leading some clinicians to initiate therapy as early as possible. When symptoms begin to interfere with daily living and become bothersome, many clinicians prefer to start with an MAO-B inhibitor or dopamine agonist, reserving carbidopa/levodopa for patients with moderate to severe symptoms. The decision on when to start treatment and which treatment to use is best individualized, taking into account the patient’s symptoms and concomitant medications, as well as drug efficacy, potential for disease modification, and tolerability. Comprehensive management of PD also includes management of nonmotor symptoms and adverse effects of PD medications. Pharmacists can play an important role in ensuring that symptoms are optimally controlled while preventing, recognizing, and managing adverse effects and drug interactions.

Answers to “Think It Through”
The following are suggestive of early PD in this case:
Age, RBD, the OTC laxative and fiber supplement (suggesting that the patient is constipated), her reported feeling of “slowing down” (which could be bradykinesia), and muscle stiffness and back pain (which could be effects of rigidity).

Answers to “What Do You Think?”
No treatment has definitively been proven to be neuroprotective, therefore clinicians must form their own opinions about the risk:benefit ratio of early therapy. Advantages of early therapy might include delay in progression of disability, reduction in PD symptoms, and maximized function. The disadvantages include possible adverse effects for specific medications, the cost of the medication, and the challenges of adherence to the medication. Pharmacists can work with patients and physicians to help identify the best therapy for specific patients and manage these issues. Treatment of mild to moderate symptoms is often prudent when symptoms begin to interfere with daily activity.

References
5. Lew M. Overview of Parkinson’s Disease. 2007;27(pt 2):155S–60S.
29. Olanzapine odt, full prescribing information from U.S. FDA regarding Neurontin (gabapentin) [package insert]. Olanzapine odt, full prescribing information from U.S. FDA regarding Neurontin (gabapentin) [package insert].
1. Motor symptoms of PD become apparent:
   a. Approximately 6 years before nonmotor symptoms develop.
   b. After an estimated 70% to 80% of dopaminergic neurons are lost.
   c. In parallel with nonmotor symptoms, because both are tied to loss of dopaminergic neurons.
   d. Before deterioration of dopaminergic neurons in the substantia nigra.

2. A pharmacist should evaluate further for PD by asking about other early PD symptoms in a patient who presents with:
   a. Rapid eye movement sleep behavior disorder.
   b. Urinary retention.
   c. Hallucinations.
   d. Headache.

3. Tremor is more likely to be a symptom of PD than of essential tremor in a patient whose tremor:
   a. Has a bilateral presentation.
   b. Is more prominent when the patient is still or at rest.
   c. Is the only symptom.
   d. Does not respond to carbidopa/levodopa.

4. Which of these PD therapies is a dopamine precursor that is converted to dopamine in the brain?
   a. Pramipexole.
   b. Selegiline.
   c. Amantadine.
   d. Levodopa.

5. Which of the following investigational therapies is being developed as monotherapy for early PD, among other uses?
   a. Safinamide.
   b. Sumanirole.
   c. Pardoprunox.
   d. Lisuride.

6. Which of the following clinical trial designs has been used to evaluate disease modification in PD?
   a. Proof-of-concept design.
   b. Factorial design.
   c. Crossover design.
   d. Washout design.

7. Which of the following PD therapies showed evidence of disease modification when used at its FDA-approved dose in two delayed-start trials of early PD?
   a. Pramipexole.
   b. Ropinirole.
   c. Rasagiline.
   d. Selegiline.

8. Neuroimaging trials suggest a faster rate of decline in dopaminergic activity in the nigrostriatum with:
   a. Ropinirole versus levodopa.
   b. Pramipexole versus levodopa.
   c. Levodopa versus pramipexole.
   d. Selegiline versus levodopa.

9. A patient expresses interest in using OTC supplements for PD and asks if there is any proof that they work. What alternative therapy has been shown in a randomized phase III clinical trial to provide neuroprotection in PD?
   a. Vitamin E.
   b. Coenzyme Q10.
   c. Creatine.
   d. To date, none have been identified.

10. The most effective therapy for relief of characteristic motor symptoms of PD is:
    a. Carbidopa/levodopa.
    b. A dopamine agonist.
    c. An MAO-B inhibitor.
    d. An anticholinergic agent.

11. Motor complications such as dyskinesia, “on-off” episodes, and wearing off effects occur in many patients taking which PD therapy long term?
    a. Dopamine agonists.
    b. MAO-B inhibitors.
    c. COMT inhibitors.
    d. Carbidopa/levodopa.
12. Leg edema is an adverse effect of which of the following PD therapies?
   a. Carbidopa/levodopa.
   b. Dopamine agonists.
   c. Anticholinergic agents.
   d. MAO-B inhibitors.

13. Both the “cheese reaction” and serotonin syndrome are most likely to occur in patients taking:
   a. COMT inhibitors.
   b. Therapies that inhibit MAO type A, including nonselective MAO inhibitors.
   c. Selective MAO type B inhibitors.
   d. Carbidopa/levodopa.

14. A patient with PD taking carbidopa/levodopa complains of nausea. Which represents the best recommendation to this patient for relief of nausea?
   a. Increase fluid intake and dietary fiber.
   b. Take the carbidopa/levodopa 1 hour before eating.
   c. Increase caffeine intake if not contraindicated.
   d. Ingest ginger products.

15. A patient with PD develops psychosis thereby making it necessary to reduce the dose and/or gradually discontinue her PD medications. Which of these agents should be discontinued last?
   a. Carbidopa/levodopa.
   b. Dopamine agonist.
   c. Anticholinergic agent.
   d. MAO-B inhibitor.

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