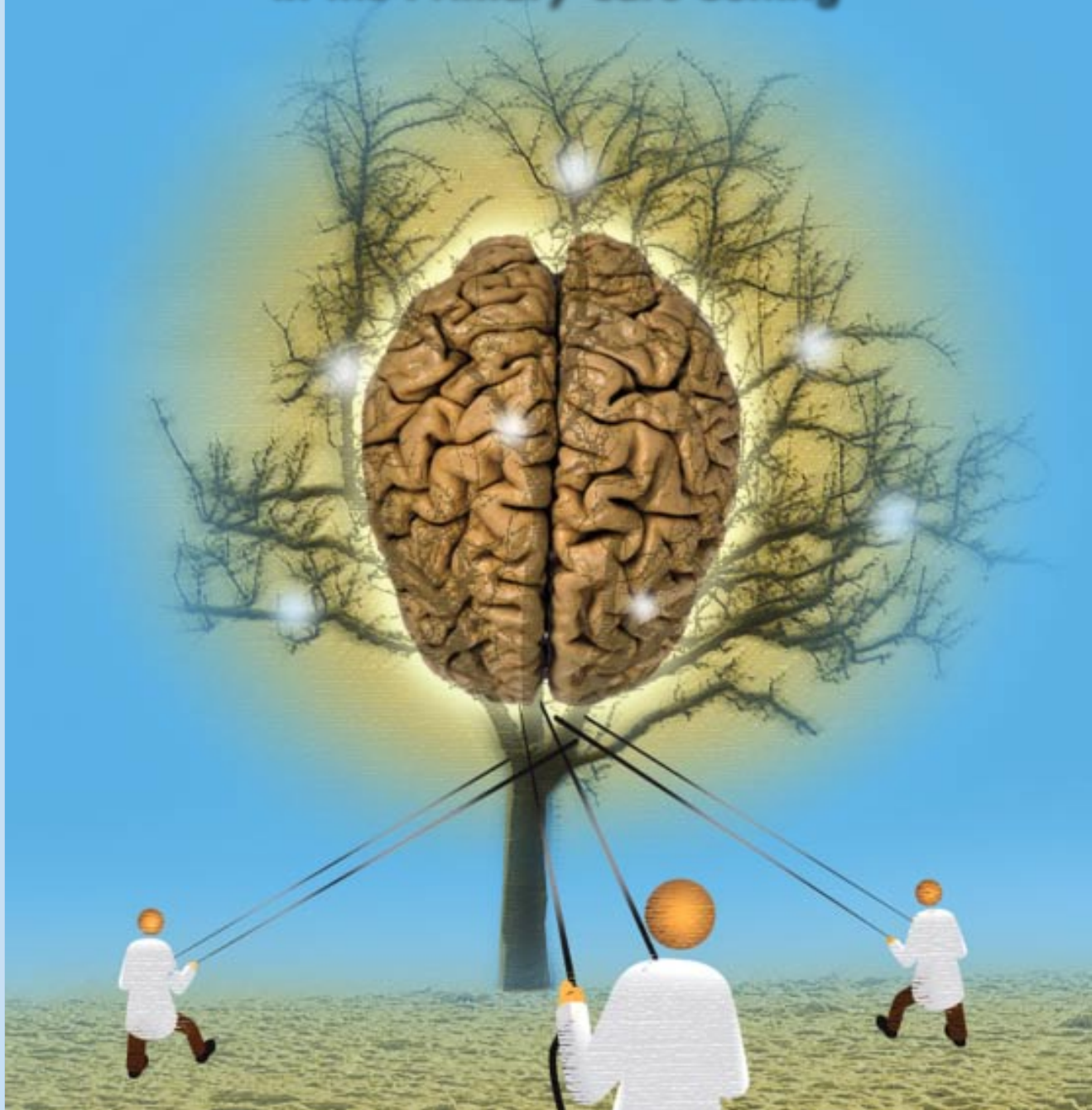


A Self-Study Supplement to

# Clinician Reviews®

A CME/CPE/CE Activity

## The Management of Parkinson's Disease in the Primary Care Setting



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## Statement of Need

Parkinson's disease (PD) is chronic and progressive, and poses numerous challenges for health care providers. Future projections estimate the worldwide number of confirmed PD patients could climb to 9.3 million by 2030, a number that does not include individuals who have acquired PD without knowing it and are not receiving treatment.

Although PD can be managed, current pharmacotherapies only control symptoms. Since there is no cure, early detection and diagnosis of PD is critical. Primary care practitioners (PCPs)—typically the first health care provider a patient sees—will be expected to identify the initial, subtle nonmotor symptoms of PD, which may precede obvious motor symptoms by years. And, in today's managed care model, PCPs oversee multiple aspects of a patient's health care needs, from differentiating PD from other forms of parkinsonism, administering medications, working with neurologists, and monitoring disease progress.

PCPs need to be aware of current pharmacotherapies, adverse events associated with these medications, and when PD patients should be referred to neurologists. Ongoing education in diagnosis and treatment strategies of PD is needed for PCPs to optimally manage their PD patients' health problems that are both related and unrelated to PD throughout the course of the disease.

This monograph will provide information for PCPs on the diagnosis and management of patients with PD, including established treatment guidelines and pharmacologic options for use in everyday clinical practice.

## Target Audience

This activity is designed for primary care physicians, physician assistants, nurses, pharmacists, and nurse practitioners who treat Parkinson's disease.

## Learning Objectives

At the conclusion of this activity participants should be able to:

- Identify the cardinal symptoms of PD and differentiate it from other movement disorders
- Compare the primary pharmacotherapeutic agents and develop specific treatment strategies to initiate therapies
- Develop physician-patient communication techniques to help determine patients' current medications to avoid drug-drug interactions
- Review referral algorithms for physical, speech, and occupational therapy as warranted as the disease advances

## Faculty

### Burton L. Scott, MD, PhD

Co-Activity Director  
Associate Clinical Professor of Medicine  
Department of Neurology  
Duke University Medical Center  
Durham, North Carolina

### Mark A. Stacy, MD

Co-Activity Director  
Associate Professor of Clinical Medicine  
Department of Neurology  
Duke University Medical Center  
Durham, North Carolina

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## Contact Information

For technical questions:  
TCL Institute, LLC  
104 Towerview Court  
Cary, NC 27513  
919-467-0006 x 233  
215-243-7273 (fax)  
[cme@tclinstitute.com](mailto:cme@tclinstitute.com)

For questions regarding credit:  
Duke University School of Medicine  
Office of Continuing Medical Education  
DUMC Box 104500  
3100 Tower Boulevard, Suite 1300  
Durham, NC 27707  
919-401-1200  
919-401-1213 (fax)  
[cme@mc.duke.edu](mailto:cme@mc.duke.edu)

## Introduction

As a progressive neurologic disorder that impairs nerve cells in portions of the brain that control movement, Parkinson's disease (PD) is the second most common neurodegenerative disorder in the United States, exceeded only by Alzheimer's disease.<sup>1,2</sup> Because it limits patients' functional and nonmotor abilities, PD imposes considerable physical, economic, and emotional burdens.<sup>3</sup> Patients endure substantial disability, deficits in health-related quality of life (HRQOL), and increased risk of earlier mortality.<sup>4,5</sup>

PD is generally characterized by four primary clinical motor symptoms: resting tremor, bradykinesia, rigidity, and postural instability; however, resting tremor may be absent and postural instability may occur late in the course of the disease.<sup>1</sup> Moreover, flexed posture and freezing (motor blocks) are hallmark symptoms of parkinsonism and are also regarded as motor features of PD.<sup>1,6</sup> Nevertheless, motor symptoms are not the only manifestations of PD; patients may exhibit multiple nonmotor features, including (but not limited to) depression, cognitive disorders, anxiety, dementia, autonomic disturbances, sleep abnormalities, constipation, orthostatic hypotension, anosmia (reduced sense of smell), fatigue, and weight loss.<sup>1,2,4,7</sup> PD-associated pain—muscle cramps or tightness in the neck, back, and legs; a dull pain in the head and neck; painful dystonias (especially in the feet); and neuropathic pain consisting of burning pain, tingling, or numbness—affects a significant minority of patients and often goes unrecognized either because patients do not associate pain with PD or because primary care practitioners (PCPs) do not ask PD patients about pain.<sup>8,9</sup>

## Early Diagnosis of PD Improves Long-Term Treatment Success

Early diagnosis is essential to optimally managing PD.<sup>10</sup> Early diagnosis currently enables clinicians to initiate medical treatment as soon as clinical changes associated with PD are detected. If safe, efficacious treatments with disease-modifying or neuroprotective capabilities become available, identifying individuals before motor symptoms are apparent will be a major priority, since starting neuroprotective therapy too late may negate the therapy's ability to stop the degenerative process.

Identifying PD patients, referring them to specialists when appropriate, and providing affordable, effective treatment are substantial public health challenges. PCPs play a crucial role because they manage multiple health care needs—detecting PD, distinguishing PD from other forms of parkinsonism, administering medications, collaborating with specialists, treating comorbidities, and monitoring disease progress.<sup>11</sup>

Detecting subtle nonmotor symptoms and implementing potential disease-modifying therapies can improve outcomes.<sup>10,12</sup> The clinical presentation of PD varies among patients and can be misdiagnosed in the disease's early stages.<sup>4</sup> PD symptoms may go unrecognized for years by patients and their physicians. Of the estimated 1 million Americans who have PD, nearly 20% display no resting tremor—one of the cardinal symptoms of PD.<sup>4,13</sup> Many PD patients do not display other common signs of the disease—shuffling gait, freezing, and falls—until long after the loss of most dopaminergic neurons. Thus, early diagnosis relies on careful history taking and physical examination, two duties usually performed first by PCPs.

PCPs may need to differentiate PD from other neurodegenerative diseases with parkinsonian features and to make pharmacotherapy decisions requiring an understanding of drug-drug interactions and adverse event profiles of numerous medications.<sup>11,14,15</sup> For example, by paying close attention to anomalies during a physical examination and by conducting a thorough medical, occupational, and medication history (both past and present), PCPs are well-positioned to distinguish PD from parkinsonian features caused by exposure to antiemetics, antipsychotics, toxins (eg, carbon monoxide, mercury, manganese, methanol, ethanol), or illegal “designer” drugs (eg, methylphenyltetrahydropyridine).<sup>11</sup>

However, recent evidence suggests that a gap exists between established guidelines for PD management and actual practice.<sup>16</sup> A 2007 survey of 370 physicians and allied health care providers shed light on this gap. The surveyed clinicians completed a questionnaire to determine their compliance with established guidelines for PD management. The compliance rate among neurologists was 73.0%, while PCPs and allied health care providers recorded compliance rates of 48.3% and 45.6%, respectively.

## Prevalence, Impact, and Epidemiology of PD

Although estimating the prevalence of PD is inexact because other forms of parkinsonism are frequently misdiagnosed as PD, current and projected data offer clues to the present and future impact of PD.<sup>1</sup>

One systematic review projects that the number of PD cases will reach 8.67 million worldwide by 2030.<sup>17</sup> According to current estimates, costs associated with PD already exceed \$20 billion annually in the United States.<sup>18</sup>

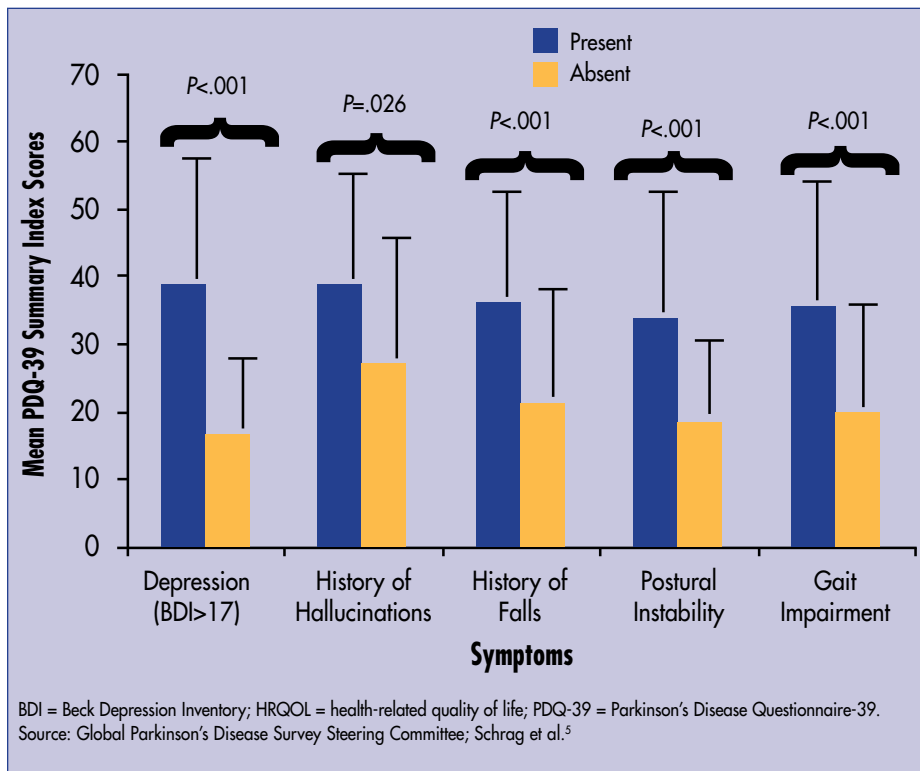
PD most often becomes apparent when patients are in their fifties and early sixties, although up to 10% of those affected are 45 or younger.<sup>4</sup> In the Rotterdam study of 6839 participants, the incidence of parkinsonism and PD was found to be 0.5 per 1000 person-years in subjects aged 55 to 65 years and climbed steadily for participants aged 85 and older to 5.3 per 1000 person-years.<sup>19</sup>

A study of 588 newly diagnosed cases of PD revealed that the incidence rate for men (19.0 per 100,000 person-years; 95% confidence interval [CI], 16.1–21.8) was higher than for women (9.9 per 100,000 person-years; 95% CI, 7.6–12.2).<sup>20</sup> PD incidence may also vary by race and ethnicity. The age- and gender-adjusted incidence rate of PD was highest in Hispanics at 16.6 per 100,000 (95% CI, 12.0–21.3), followed by non-Hispanic whites (13.6 per 100,000 person-years; 95% CI, 11.5–15.7), Asians (11.3 per 100,000 person-years; 95% CI, 7.2–15.3), and African Americans (10.2 per 100,000 person-years; 95% CI, 6.4–14.0).

## Pathogenesis

PD results from substantial loss of dopaminergic neurons from the substantia nigra portion of the midbrain, which in turn depletes dopamine in the striatum, the synaptic target of the depleted substantia nigra neurons.<sup>21</sup> Genes, environmental factors, and endogenous toxins from cellular oxidative reactions have all been cited as potential causative factors.<sup>2,22</sup> Susceptibility genes coordinating with environmental agents may initiate the process of dopamine neuron death in the substantia nigra. Exposure to pesticides, herbicides, solvents, and welding materials; rural living; and drinking well water are also cited as potential triggers.<sup>2</sup>

**Figure 1. Symptoms Associated With Worsening HRQOL**



## Nonmotor Features of PD

Despite the emphasis on managing motor symptoms in clinical practice, evidence suggests that the nonmotor symptoms of PD have greater significance when assessed by HRQOL measures, institutionalization rates, or health economics.<sup>5,12</sup> Unfortunately, there is little evidence to suggest that dopaminergic drugs that are typically used to treat the motor symptoms associated with PD are efficacious in treating the nonmotor symptoms.<sup>12</sup>

### Depression and PD

Depression is the most common neuropsychiatric disorder associated with PD, affecting up to half of patients.<sup>4</sup> Often unrecognized, depression can be an integral part of the disease or a reaction to it; it can cause sleep disruption and other unexplained symptoms.<sup>4,7</sup> Anxiety may accompany depression or progressive cognitive impairment. Typical manifestations of depression include apathy, psychomotor retardation, memory impairment, pessimism, irrationality, and suicidal thoughts.<sup>7</sup> Depressed parkinsonian patients may express less guilt and self-reproach than do those with primary depression, but they may also display more irritability, sadness, and concern about their health.

A survey of 92 patients classified as having “probable PD” demonstrated that depression (as measured by the Beck Depression Inventory [BDI], a 21-item index to measure severity of depression; a score of 17 [out of a maximum 63] was the cutoff point for moderate to severe depression) is the strongest predictor of poor HRQOL in PD (Figure 1).<sup>5</sup> Surveyed patients completed the Parkinson's Disease Questionnaire-39 (PDQ-39), a 39-item disease-specific QOL questionnaire for PD patients, and the BDI to identify the factors that deter-

mine QOL in PD patients. Higher PDQ-39 scores indicate worsening QOL.

### Constipation

Constipation should raise the index of suspicion of PD for PCPs. A prospective study assessing the bowel habits of 6790 men aged 51–75 years without PD for 24 years showed that men with constipation (<1 bowel movement per day) carried 2.7 times the risk of developing PD compared to those who had 1 bowel movement per day (95% CI, 1.3–5.5;  $P=.007$ ).<sup>23</sup>

### Olfactory Deficits

Selective olfactory deficits independent of disease severity and duration occur in 70% to 90% of patients with PD.<sup>24</sup> In a 2003 study of 49 nondemented patients with PD and 52 age- and sex-matched controls, Double and colleagues noted that the ability to identify five specific odors was more affected in PD patients (gasoline, banana, pineapple, smoke, and cinnamon), although PD patients' ability to detect seven other odors included on the test was no different than that of controls.

### Sleep Disorders

Evidence suggests that sleep disturbances start early in PD.<sup>12</sup> Sleep behavior disorders can herald the onset of motor signs in up to 40% of PD patients. Bed partners of PD patients have reported that patients talk, shout, or make threats during sleep; in addition, arm or leg jerks, falling out of bed, and violent assaults have been reported.

Although sleep disturbances were once blamed on pharmacological therapy, researchers now believe they are a core aspect of PD. Approximately 70% of PD patients have some form of sleep disruption, which usually starts early in the disease course.<sup>7,25</sup> Among PD patients, insomnia, rapid eye movement (REM) disorders, and daytime sleepiness are commonly reported sleep disorders.<sup>1</sup>

REM sleep behavior disorder (considered a preparkinsonian state) occurs in approximately one-third of PD patients and features “acting out” one's dreams.<sup>12</sup> This condition is characterized by an increase in violent dream content accompanied by talking, yelling, swearing, grabbing, punching, kicking, jumping, and other potentially dangerous motor activity that may also involve the bed partner.<sup>1,26</sup>

Excessive daytime sleepiness is important to recognize because it substantially affects QOL in PD patients. Even though excessive daytime sleepiness may contribute to fatigue, this commonly reported symptom is also experienced independently of sleepiness.<sup>1</sup> Excessive daytime sleepiness and involuntary dozing

affect up to half of PD patients and could be a preclinical marker of early PD.<sup>12,27</sup>

### Autonomic Dysfunction

Autonomic failure due to degeneration and dysfunction of autonomic nuclei may be a presenting feature of PD, although it is more typically associated with multiple system atrophy (MSA).<sup>1</sup>

Autonomic dysfunction in PD can present as dysphagia or choking, hypersalivation, impaired gastrointestinal motility, constipation, or hypotension.<sup>2,4,28,29</sup> Other manifestations include orthostatic hypotension and sweating, sphincter, and/or erectile dysfunctions.

### Cognitive and Neurobehavioral Deficits

Dementia in PD is more prevalent in patients with advanced or late-onset (after age 65) disease.<sup>7</sup> In these patients, depression, severe disease, and presence of levodopa-induced psychosis can be associated with dementia. Although they usually do not pose a significant problem for patients because they do not hinder day-to-day activities and responsibilities, subtle impairments such as bradyphrenia (slowness of thinking) and difficulty with “finding the right word” can also develop in PD.

The dementia associated with PD typically becomes apparent several years after motor features appear.<sup>7</sup> It often takes the form of memory difficulties that respond to external cues; distractibility; difficulty with planning; lack of motivation; and slowed thinking.

The Sydney Multicenter Study of Parkinson’s Disease found that 85% of the 52 patients showed cognitive decline and 48% met diagnostic criteria for dementia after 15 years of follow-up.<sup>30</sup> Another community-based prospective study found that the risk of dementia in 130 PD patients was six times that in the 1908 healthy patients.<sup>31</sup> PD-related dementia is also associated with a number of other neuropsychiatric comorbidities; in a trial of 537 patients, commonly reported adverse events included depression (58%), apathy (54%), anxiety (49%), and hallucinations (44%).<sup>32</sup>

In addition to cognitive and affective disorders, many patients with PD show features of obsessive-compulsive and impulsive behavior, such as craving for sweet foods, binge eating, compulsive foraging, hypersexuality, pathologic gambling, compulsive shopping, and intense fascination with repetitive handling, examining, sorting, and arranging of objects (known as *punding*).<sup>1,33,34</sup> These symptoms reflect a condition known as *hedonistic homeostatic dysregulation* and have been attributed to dopamine dysregulation syndrome as a result of dopamine agonists.

Anxiety disorders are also common in PD.<sup>12</sup> Anxiety can present as phobias, panic attacks, or generalized anxiety disorder and can be related to drug-induced motor fluctuations in PD patients. Apathy may be a distinct symptom of PD, independent of depression, somnolence, or fatigue. PD patients have higher levels of apathy than do equally disabled patients with osteoarthritis, which suggests a neurodegenerative contribution to this problem. Up to 40% of patients have visual hallucinations, which are often benign, whereas more worrisome symptoms—delusions, paranoia, and delirium—become more common as the disease progresses.

### Differential Diagnoses

Misdiagnosis rates for PD are as high as 24%.<sup>35</sup> One reason that diagnosis of PD is challenging is that PCPs are tasked with differentiating

PD from conditions that may have clinically similar features, including essential tremor (ET), drug-induced parkinsonism, vascular parkinsonism, and MSA. In a community-based study of 402 patients taking antiparkinsonian medication, the most common misdiagnoses were ET, Alzheimer’s disease, and vascular pseudoparkinsonism.<sup>36</sup> Moreover, many of the obvious features of PD—rigidity, gait disturbance, bradykinesia—can occur due to normal aging or from comorbid or multifactorial conditions (eg, diabetes, cancer).<sup>1,37</sup>

*Parkinsonism* is a clinical term that encompasses motor problems that may include tremor at rest in addition to rigidity and bradykinesia (slowed movement).<sup>2</sup> Although PD is the major cause of parkinsonism, several non-PD conditions have clinical features of parkinsonism. Because of the wide range of possible causative conditions, parkinsonism is divided into four subtypes:

- **Primary parkinsonism**, in which symptoms typically start on one side of the body before spreading to the other; resting tremor is often present; and there is a clinical response to levodopa therapy. Resting tremor is sometimes absent in patients with PD and is typically absent in Parkinson-plus syndromes.
- **Secondary parkinsonism**, which includes drug-induced parkinsonism and postencephalitic parkinsonism
- **Parkinson-plus syndromes**, when parkinsonism is one of several neurologic features and includes progressive supranuclear palsy and MSA. Parkinson-plus diseases (eg, corticobasal ganglionic degeneration) do not respond to levodopa.
- **Heredodegenerative disorders**, in which parkinsonism is one element of a hereditary degenerative disorder (ie, juvenile Huntington’s disease or Wilson’s disease)

### Differentiating ET From PD

Whereas *resting tremor* is a primary nonvoluntary motor feature of PD, *action tremor* refers to tremor during voluntary contraction of muscles and includes postural, isometric, and kinetic tremor.<sup>38</sup> Although ET typically features postural and action tremor but not resting tremor, ET is frequently confused with early PD. Distinguishing between ET and tremor associated with PD is crucial because the management and prognosis in the two conditions are different. Medications used to treat tremor (eg, propranolol, primidone, sotalol, atenolol, gabapentin, topiramate, alprazolam, or botulinum toxin A injections) should be titrated slowly because adverse events and tolerability are the main compliance issues.<sup>38,39</sup>

ET is characterized by the presence of bilateral, symmetrical, postural, or kinetic (action) tremor that affects the hands and forearms and is visible and persistent.<sup>35</sup> The clinical criteria for ET include<sup>38</sup>:

- Postural tremor of moderate amplitude present in at least one arm
- Tremor of moderate amplitude present in at least one arm during tasks such as pouring water or using a spoon
- Tremor must interfere with at least one activity of daily living
- Medications, hypothyroidism, alcohol, and other neurologic conditions are not the cause of the tremor

To distinguish PD-associated tremor from ET, PCPs should look for other signs of PD, especially bradykinesia and rigidity, which are normally absent in ET.<sup>38</sup> Resting tremor in patients with PD can also involve the lips, chin, jaw, and legs.<sup>1</sup> Unlike ET, resting tremor rarely involves the neck, head, or voice. Therefore, a patient presenting with head tremor probably has ET or cervical dystonia (or both), not PD.

Clinicians should observe patients sitting at rest to determine whether there is evidence of a resting tremor of the head.<sup>38</sup> Patients are instructed to stretch out their arms and hands in front of them for clinicians to look for postural tremor, and should perform finger-nose-finger movements to reveal any kinetic tremor.

**Table 1** lists features that distinguish ET from the resting tremor associated with PD.<sup>38</sup>

## Clinical Diagnosis

Clinical diagnosis of PD relies upon detection of primary motor and non-motor symptoms during patient evaluation.<sup>1</sup> PD begins insidiously and gradually worsens.<sup>2</sup> Early symptoms can be subtle in development (slowness, weakness, fatigue, decreased sense of smell, and loss of appetite, among others), yet they may precede more obvious motor symptoms.<sup>40</sup>

## Detecting Motor Features of PD

### Resting Tremor

*Resting tremor* is the most common and easily recognized sign of PD.<sup>1</sup> It is typically unilateral at onset, occurs at a frequency of 4 to 6 Hz, and usually appears in the distal part of an extremity. The classic form of resting tremor consists of a “pill-rolling” motion made with the thumb and forefinger.<sup>4</sup>

It is important for PCPs to classify tremor type.<sup>38</sup> Various types of tremor can be distinguished clinically, based upon the activation condition, frequency, and topographic distribution:

- **Resting Tremor:** Tremor that occurs in a body part that is not being voluntarily activated and that is supported against gravity
- **Action Tremor:** Tremor produced during voluntary contraction of muscle that produces postural, isometric, kinetic, or intention tremor
- **Postural Tremor:** Tremor that is present while a posture is voluntarily maintained against gravity, eg, while the arms are outstretched
- **Kinetic Tremor:** Tremor occurring during voluntary movement; it may be present during visually guided or non-visually guided movements
- **Isometric Tremor:** Tremor resulting from muscle contraction against a rigid stationary object
- **Task-Specific Tremor:** Kinetic tremor that appears or worsens during specific tasks or activities, such as handwriting

The most prevalent of these tremor types, action tremor, occurs when the arm is extended or during voluntary movements such as writing or typing.<sup>38</sup> Resting tremor occurs when patients are sitting with their arms supported in the absence of voluntary activi-

**Table 1. Features Distinguishing ET From Tremor of PD**

| Feature  | PD  | ET  |
|--|---|---|
| Tremor   | Occurs at rest, often present during walking; decreases at least transiently with posture holding or action | Present when holding a posture or with action |
| Frequency  | 3–6 Hz  | 5–12 Hz                                       |
| Distribution   | Asymmetric  | Usually symmetric                             |
| Body parts   | Hands and legs  | Hands, head, voice                            |
| Writing  | Micrographia (small handwriting)  | Tremulous                                     |
| Course   | Progressive   | Stable or slowly progressive                  |
| Family history   | Less common   | Common  |
| Other Neurologic Signs   | Bradykinesia, rigidity, decreased postural reflexes   | None  |
| Substances That Improve Tremor   | Levodopa, dopamine agonists, anticholinergics   | Alcohol, propranolol, primidone               |
| ET = essential tremor; PD = Parkinson's disease.<br>Source: Bhidayasiri. <sup>38</sup> |   |   |

ties. It increases with mental stress (eg, when the patient counts backwards) and attenuates during voluntary movements of the affected limb.

### Bradykinesia

*Bradykinesia* occurs in 80% to 90% of PD patients and is characterized as slowness of voluntary movements.<sup>4</sup> Bradykinesia is sometimes confused with akinesia and hypokinesia.<sup>41</sup> *Akinesia* is the absence of spontaneous movement in a body part or the absence of an associated movement (eg, swinging the arm during walking). *Hypokinesia* refers to decreased amplitude of voluntary movements (as with micrographia). Perceived muscle weakness, rigidity, tremor, movement variability, and slowing of thought contribute to bradykinesia in PD patients.

Bradykinesia is a hallmark of basal ganglia disorders; it encompasses difficulty with planning, initiating, and executing movement and performing sequential and simultaneous tasks.<sup>1</sup> The initial overt manifestation of bradykinesia is slowing performance of activities of daily living and other voluntary movement and slowing of reaction times. Bradykinesia intrudes upon tasks requiring fine motor control (eg, buttoning, using utensils). Other manifestations include loss of spontaneous or automatic movements and gestures, drooling due to impaired swallowing, monotonic and hypophonic dysarthria, loss of facial expression and decreased blinking, and reduced arm swing during walking.

To assess bradykinesia, clinicians should ask patients to perform rapid, repetitive, alternating movements of the hand (finger taps, hand grips, hand pronation-supination), and heel taps.<sup>1</sup> Slowness and decrementing amplitude of movements should be noted. Surprisingly, immobile patients who become excited may be able to make quick movements such as catching a ball or starting to run if they hear “Fire!” This phenomenon (*kinesia paradoxica*) suggests that patients with PD have intact motor capabilities but have trouble activating them without an external trigger to compel movement.

## Freezing

*Freezing* (also known as motor blocks) is a form of akinesia.<sup>1</sup> In a questionnaire answered by 6620 PD patients, 47% of patients reported freezing.<sup>42</sup> This problem occurred predominantly in men and less frequently in patients whose chief complaint was tremor. Freezing frequently causes falls.<sup>1</sup>

There are five subtypes of freezing: start hesitation, turn hesitation, hesitation in tight quarters, destination hesitation, and open-space hesitation.<sup>1</sup> Freezing occurs suddenly and typically affects the legs during walking, although the arms and eyelids may also be affected. Freezing includes hesitation when starting to walk (start hesitation) or an inability to move the feet during specific situations (eg, turning or walking through a narrow passage, crossing busy streets, or approaching a destination).

## Rigidity

PCPs can detect the “cogwheel” pattern of rigidity (varying intensity of resistance while the limb is passively moved) in the distal part of the patient’s limbs, most often at the wrist joint.<sup>4</sup> Cogwheel rigidity is commonly seen in patients experiencing resting tremor in the affected limb.<sup>1</sup> “Leadpipe” rigidity is uniform resistance to passive limb movement.<sup>43</sup> Rigidity may also occur at the neck, shoulders, hips, or ankles. Reinforcing maneuvers (eg, voluntary movements of the contralateral limb, known as *Froment’s maneuver*) are useful in making mild rigidity more prominent.

Rigidity may be associated with pain.<sup>1</sup> A painful shoulder can be an initial manifestation of PD, although it is more commonly caused by arthritis, bursitis, or rotator cuff injury.

## Postural Instability

Postural instability is a sign of more advanced PD.<sup>1</sup> Postural instability due to loss of postural reflexes is generally a manifestation of later stages of PD and usually occurs after the onset of other clinical features. Postural instability, along with freezing of gait, is the most common cause of falls and contributes significantly to the risk of hip fracture.<sup>1,44</sup>

The pull test, in which the patient is informed about what to expect and then briskly pulled backward or forward at the shoulders, is used to assess the degree of retropulsion or propulsion.<sup>1</sup> Taking more than two steps backward (or absence of postural response) is abnormal.

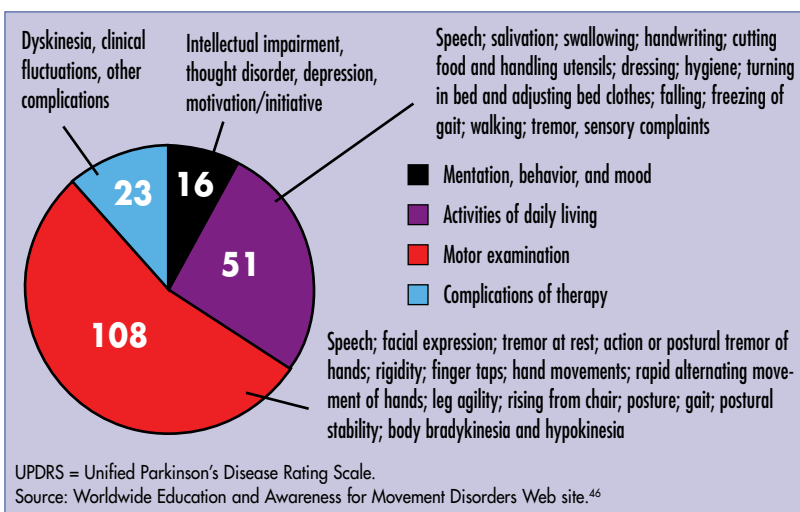
## Rating Scales to Aid PCP-Patient Communication and Assess Disease Progression

Clinicians use rating scales to evaluate the progression of motor impairment and physical disability in PD patients, and monitor response to treatment.<sup>45</sup>

### Unified Parkinson’s Disease Rating Scale

The Unified Parkinson’s Disease Rating Scale (UPDRS) is the most widely used clinical rating scale for PD.<sup>45</sup> The scale consists of four sections evaluating behavior and mood, activities of daily living, motor symptoms, and complications of therapy (Figure 2).<sup>46</sup>

Figure 2. UPDRS Points Distribution



The sections on behavior and mood, activities of daily living, and motor symptoms comprise individual items scored on a 5-point scale, from 0 (no disability) to 4 (maximum disability), with a maximum score of 175 for the three sections.<sup>45,46</sup> The fourth section of the scale evaluates patients with more advanced disease who are receiving pharmacotherapies.

The UPDRS can be applied across all clinical stages of PD and includes a fairly comprehensive assessment of motor symptoms.<sup>47</sup> Nevertheless, key weaknesses of the UPDRS include ambiguities in response-scale descriptors, poor interrater reliability for some items, and a lack of items assessing nonmotor aspects of PD.

### MDS-UPDRS—A Response to the Shortcomings of the UPDRS

A working group composed of thought leaders and clinicians within the Movement Disorder Society (MDS) revised the UPDRS to enable clinicians to better detect subtle changes in function associated with progression of PD.<sup>45</sup> The revised version was named the “MDS-UPDRS.”

The MDS-UPDRS retains the four-part structure and the total score of the UPDRS but also integrates key nonmotor features.<sup>45</sup> As in the UPDRS, the items are evaluated on a 5-point scale (0 = normal; 4 = severe). Experienced PCPs can complete the MDS-UPDRS in 30 minutes or less.

The MDS-UPDRS contains 50 questions divided across four parts: nonmotor aspects of experiences of daily living, motor experiences of daily living, motor examination, and motor complications, as shown in Table 2.<sup>45</sup>

### Hoehn and Yahr Scale

The Hoehn and Yahr scale is a widely used broad classification scheme for grading disease severity in PD.<sup>48</sup> Its stages range from 0 (no signs of disease) to 5 (symptoms on both sides of body and wheelchair-bound or confined to bed unless assisted).<sup>1</sup>

Each stage of the Hoehn and Yahr scale is described below<sup>49</sup>:

- **Stage 1:** Main symptoms (tremor, muscle stiffness, slowness of movement, and problems with posture) are on one side of the body
- **Stage 2:** Disease is on both sides of the body and minor symptoms (problems with swallowing, talking, and “facial masking” [loss of facial expression]) may appear

**Table 2. MDS-UPDRS Assessments**

| Part I: Nonmotor Aspects of Experience of Daily Living  | Part II: Motor Experiences of Daily Living   | Part III: Motor Examination   | Part IV: Motor Complications   |
|---|--|---|--|
| <ul style="list-style-type: none"> <li>• Cognitive impairment</li> <li>• Hallucinations and psychosis</li> <li>• Depressed mood</li> <li>• Anxious mood</li> <li>• Apathy</li> <li>• Features of dopamine dysregulation syndrome</li> <li>• Sleep problems</li> <li>• Daytime sleepiness</li> <li>• Pain and other sensations</li> <li>• Urinary problems</li> <li>• Constipation problems</li> <li>• Lightheadedness on standing</li> <li>• Fatigue</li> </ul> | <ul style="list-style-type: none"> <li>• Speech</li> <li>• Saliva and drooling</li> <li>• Chewing and swallowing</li> <li>• Eating tasks</li> <li>• Dressing</li> <li>• Hygiene</li> <li>• Handwriting</li> <li>• Doing hobbies and other activities</li> <li>• Turning in bed</li> <li>• Tremor impact on activities</li> <li>• Getting in and out of bed</li> <li>• Walking and balance</li> <li>• Freezing</li> </ul> | <ul style="list-style-type: none"> <li>• Speech</li> <li>• Facial expression</li> <li>• Rigidity</li> <li>• Finger tapping</li> <li>• Hand movements</li> <li>• Pronation-supination movements of hands</li> <li>• Toe tapping</li> <li>• Leg agility</li> <li>• Arising from chair</li> <li>• Gait</li> <li>• Freezing of gait</li> <li>• Postural stability</li> <li>• Posture</li> <li>• Global spontaneity of movement (body bradykinesia)</li> <li>• Postural tremor of hands</li> <li>• Kinetic tremor of hands</li> <li>• Rest tremor amplitude</li> <li>• Constancy of rest tremor</li> </ul> | <ul style="list-style-type: none"> <li>• Dyskinesias: time spent with dyskinesias</li> <li>• Dyskinesias: functional impact of dyskinesias</li> <li>• Dyskinesias: painful "off"-state dystonia</li> <li>• Motor fluctuations: time spent in the "off" state</li> <li>• Motor fluctuations: functional impact of fluctuations</li> <li>• Motor fluctuations: complexity of motor fluctuations</li> </ul> |

MDS-UPDRS = Movement Disorder Society version of the Unified Parkinson's Disease Rating Scale. Source: Goetz et al.<sup>45</sup>

- **Stage 3:** The same symptoms of stage 2 are present but may be worsening. Problems with balance are noticeable, but patient is still independent.
- **Stage 4:** Patient is now becoming more disabled and needs help with some or all activities of daily living. Balance is worsening.
- **Stage 5:** Patient is confined to a wheelchair or bed and needs total assistance

### Measuring Nonmotor Symptoms

There are two scales frequently used to measure nonmotor symptoms: Scales for Outcomes in Parkinson's Disease–Psychiatric Complications (SCOPA-PC) and Nonmotor Symptom (NMS) screening questionnaire (NMSQuest).<sup>50,51</sup>

SCOPA-PC measures hallucinations, illusions, paranoid ideation, altered dream phenomena, confusion, sexual preoccupation, and compulsive behavior.<sup>50</sup> Each item is rated on a scale of 0 (no symptoms) to 3 (severe symptoms), with a total score ranging from 0 to 21.

NMSQuest consists of 30 questions in nine domains.<sup>51</sup> The domains are digestive, urinary, apathy/attention/memory, hallucinations/delusions, depression/anxiety, sexual function, cardiovascular, sleep disorders, and miscellaneous.

### QOL Measures

Because nonmotor clinical features of PD can be as disabling as motor symptoms (if not more so), focusing only on motor symptoms does not address a major portion of the deleterious effects of PD.<sup>52</sup>

Measures that assess HRQOL provide a way to determine the overall efficacy of a specific treatment and the impact of the disease.<sup>52-57</sup> PCPs can use HRQOL measurement scales to complement objective assessments by evaluating physical, emotional, and social functioning.

Multiple HRQOL scales are available for clinicians and listed in **Table 3**.<sup>52-57</sup>

A systematic review evaluated the efficacy of HRQOL scales in 20 clinical studies of PD published between 1965 and 2000.<sup>52</sup> The study concluded that the PDQ-39, the Parkinson's Disease Quality of Life Questionnaire (PDQL), Parkinson's Impact Scale (PIMS), and Parkinson Quality of Life Questionnaire (PLQ) all had acceptable internal consistency.

PIMS takes about 10 minutes to administer, while PDQ-39, PDQL, and PLQ take 15 to 20 minutes.<sup>52</sup> In addition, content validity was satisfactory for the PDQ-39, PDQL, and PLQ. The authors also concluded that the PDQ-39 was the most valuable HRQOL assessment tool because of its validity, clinimetric

characteristics, and availability in multiple languages.

### Treatment of PD

The goal of PD therapy is evolving from controlling neurological symptoms to modifying disease progression.<sup>3</sup> Emerging therapeutic agents have demonstrated possible neuroprotective effects in cell culture and animal studies. If similar effects of medications can be extended to patients, improved long-term patient outcomes and overall treatment success can be expected.

At present, no pharmacologic agent has proven to be “neuroprotective,” so treatment continues to focus upon addressing symptoms of disease.<sup>18</sup> The primary goal of current pharmacotherapy is to restore depleted stores of dopamine by enhancing delivery to the brain of the dopamine precursor levodopa (also called “L-dopa”) using dopa-decarboxylase inhibitors (DDIs) or catechol-*O*-methyltransferase (COMT) inhibitors.<sup>58</sup> In addition, dopamine agonists and monoamine oxidase-B (MAO-B) inhibitors provide symptomatic benefits.<sup>18,59</sup>

**Figure 3** illustrates mechanisms of therapeutic drug benefits in PD.<sup>60</sup>

### Timing of Therapy

Timing the onset of therapy remains a point of debate among researchers.<sup>18</sup> Some clinicians start treatment of mild symptoms upon diagnosing PD, while others delay treatment until necessary to postpone the end-of-dose “wearing off” phenomenon observed with several PD drugs.

The Earlier Versus Later Levodopa Therapy in Parkinson Disease (ELLDOPA) trial was designed to evaluate the effects of levodopa on the progression of PD.<sup>61</sup> The results were mixed. In the ELLDOPA study, 361 patients who had never been treated with (nor required) dopaminergic drugs were randomized to receive placebo or carbidopa (at a dosage of 37.5, 75.0, or 150.0 mg/day) plus levodopa (at a dosage of 150, 300, or 600 mg/day) for 40 weeks, followed by a 2-week washout. The total postwashout UPDRS score increased 7.8 points with placebo versus 1.9 points with each of the two lower dosages of levodopa; it decreased 1.4 points with the highest dose ( $P < .001$ ). Freezing was seen primarily in the patients receiving placebo, while wearing off (29.7%) and dyskinesias (16.5%) were more common in the 91 patients receiving levodopa 600 mg/day. Patients receiving the highest dosage of levodopa had significantly more hypertension, infection, headache, and nausea than did those receiving placebo.

**Table 3. HRQOL Measurement Scales**

| Measure   | Number of Items in Questionnaire          | Description of Items Addressed  |
|---|---|---|
| Parkinson's Disease Questionnaire-39 (PDQ-39)   | 39  | Mobility, activities of daily living, emotional well-being, stigma, social support, cognition, communication, bodily discomfort                   |
| PDQ-8   | 8   | Same as PDQ-39  |
| Parkinson's Disease Quality of Life Scale (PDQUALIF)  | 33  | Social function, self-image, sexuality, sleep patterns, outlook, physical function, independence, urinary function, plus one item of global HRQOL |
| Parkinson's Disease Quality of Life Questionnaire (PDQL)  | 37  | Parkinsonian symptoms, systemic symptoms, emotional function, social function   |
| Parkinson's Impact Scale (PIMS)   | 10 (completed three times, 1 month apart) | Self-positive, self-negative, family, community, work, travel, leisure, safety, financial security, sexuality                                     |
| Parkinson Quality of Life Questionnaire (PLQ)*  | 44  | Depression, physical achievement, concentration, leisure, restlessness, activity limitation, insecurity, social integration, anxiety              |
| <small>* Validated in German only<br/>           HRQOL = health-related quality of life.<br/>           Sources: Marinus et al<sup>92</sup>; Jenkinson et al<sup>53</sup>; Peto et al<sup>54</sup>; Welsh et al<sup>55</sup>; de Boer et al<sup>56</sup>; Calne et al.<sup>57</sup></small> |   |   |

Some clinicians prefer to delay levodopa therapy for PD until clinically significant disability or functional impairment occurs.<sup>18</sup> For mildly affected patients, non-levodopa therapy (ie, amantadine or MAO-B inhibitors) is available. The reluctance to start levodopa therapy early in the disease reflects concerns about the adverse events and long-term consequences of these agents. Adverse events, including sedation, nausea, and orthostatic hypotension, can become more disabling than the motor impairment.

Whether clinicians adopt a higher or lower threshold for initiating treatment, maintaining functionality for as long as possible is the goal of clinical management.<sup>18</sup> Maintaining functioning not only improves patients' HRQOL but also reduces direct costs associated with office visits and lessens indirect costs by mitigating dependence on caregivers and requiring less time off from work.

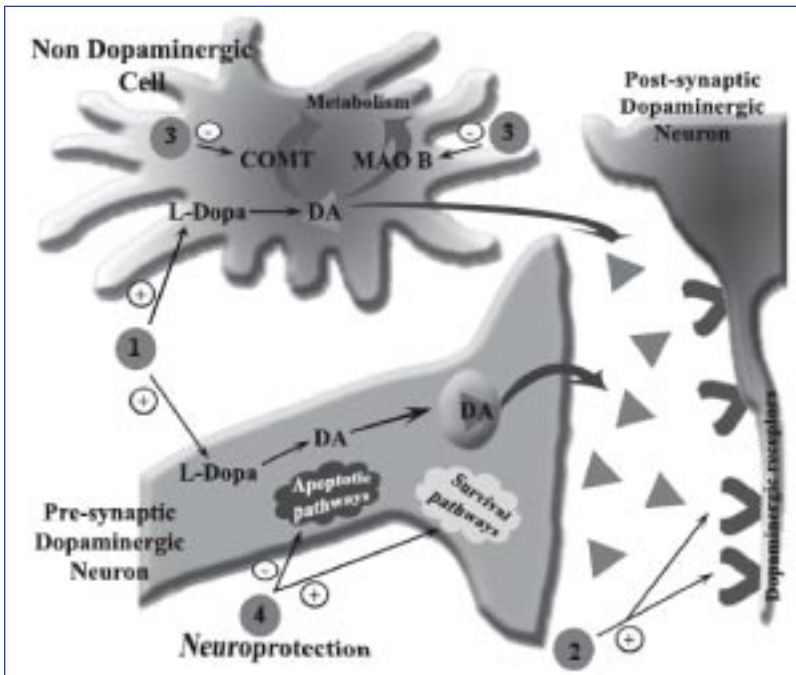
### Types of Agents

#### Levodopa

Dopamine replacement with levodopa has remained the cornerstone of antiparkinsonian drug therapy since its introduction in the late 1960s.<sup>59</sup> Because levodopa is rapidly metabolized in the systemic circulation by dopa-decarboxylase before it crosses the blood-brain barrier, levodopa is usually administered as combination therapy with a DDI, such as carbidopa or benserazide, to reduce peripheral conversion and increase availability of levodopa in the brain.

In most cases, PD patients have clinically significant positive responses to levodopa administered three times daily; ben-

**Figure 3. Interaction of Pharmacotherapies With the Brain**



1 = Dopamine precursor levodopa; 2 = Dopamine receptor agonists; 3 = Dopamine metabolizing enzymes (COMT and MAO-B) inhibitors; 4 = Neuroprotective compounds; ⊕ = Increase in the synaptic dopamine or stimulation of dopamine receptors and survival pathways; ⊖ = Inhibition of dopamine metabolizing enzymes or apoptotic pathways; ▷ = Dopamine neurotransmitter.

COMT = catechol-O-methyltransferase; DA = dopamine; L-Dopa = levodopa; MAO-B = monoamine oxidase B  
Source: Reprinted from *Therapeutics and Clinical Risk Management*, 3, Lecht S, Haroutiunian S, Hoffman A, Lazarovici P, Rasagiline – a novel MAO B inhibitor in Parkinson's disease therapy, 467-474, Copyright (2007), with permission from Dove Medical Press Ltd.<sup>60</sup>

efits are usually experienced for more than 5 years.<sup>60</sup> However, as levodopa treatment continues, motor complications usually occur.<sup>59</sup> Although levodopa effectively counters the motor features of PD initially, many patients eventually develop dyskinesias and motor fluctuations. Dyskinesia is related to the patient's age and to the dose and duration of levodopa treatment; younger patients and those with advanced disease carry a higher risk for developing dyskinesias.

Motor fluctuations that occur when the effects of individual doses of levodopa wane and enable symptoms to return in advance of the next dose are termed the "wearing off" effect.<sup>18</sup> Another form of motor fluctuations known as the "on/off effect" is characterized by sometimes sudden and unpredictable cycling between periods of normal function and periods of poor motor function.

Other adverse events associated with levodopa include nausea, sedation, vomiting, and orthostatic hypotension at the beginning of therapy; delusions, hallucinations, vivid dreams, and sleep disturbances can occur with chronic therapy.<sup>18</sup> Suddenly stopping therapy can result in the return of parkinsonian symptoms and the potential for neuroleptic malignant syndrome (fever, rigidity).

Despite concerns about early levodopa use being harmful, clinical data suggest that levodopa may slow the progression of PD and that it has a prolonged effect on the symptoms of the disease.<sup>61</sup> These positive effects are tempered by neuroimaging data suggesting decreased dopamine in nerve terminals in the presence of levodopa.

## COMT Inhibitors

COMT inhibitors (eg, entacapone, tolcapone) reduce breakdown of levodopa in the periphery, thereby allowing increased concentrations of levodopa to reach the brain for conversion to dopamine.<sup>59</sup> Because they increase peripheral dopamine concentrations when administered with levodopa, COMT inhibitors are associated with adverse events similar to those reported with levodopa, including dyskinesia, nausea, and vomiting. Also, hepatotoxicity is associated with tolcapone (but not entacapone), and patients taking tolcapone must give informed consent and take twice-monthly hepatic function tests for 6 months.<sup>18</sup>

## Dopamine Receptor Agonists

Dopamine receptor agonists were developed as complementary therapy to levodopa for treatment of motor fluctuations.<sup>18</sup> The more recently introduced nonergot agonists are also approved for initial monotherapy and are often administered as part of a treatment strategy designed to delay initiation of levodopa therapy.<sup>14,18</sup> Clinical studies have demonstrated that when administered as monotherapy or as adjunct therapy to levodopa, medications such as pramipexole, ropinirole, and rotigotine allow reduced administration of levodopa, improve motor symptoms, and improve ability to perform activities of daily living in patients who initiate therapy early.<sup>14,18,59</sup>

Adverse events of dopamine agonists include postural hypotension, somnolence, hallucinations, and impulse control disorders.

## MAO-B Inhibitors

Evidence-based guidelines established by the American Academy of Neurology and the MDS state that MAO-B inhibitors provide symptomatic benefit when used as initial monotherapy in early-stage PD and may be considered as initial therapy before administration of dopaminergic agonists.<sup>15,62</sup> MAO-B inhibitors (eg, selegiline, rasagiline) reduce breakdown of dopamine in the brain, thus increasing the supply of dopamine.<sup>18</sup> Treatment with MAO-B inhibitors has also been employed by some neurologists as a potential disease-modifying strategy.<sup>63</sup>

The Deprenyl and Tocopherol Antioxidative Therapy of Parkinsonism (DATATOP) study was designed to investigate the potential for selegiline to modify the disease course in early PD.<sup>63</sup> Evaluations of the 800 patients began in 1987 and continued until 1995, making DATATOP the largest and longest prospective controlled study of PD pharmacotherapies ever conducted.<sup>63,64</sup> The 800 patients were randomly assigned to receive either placebo pills; tocopherol 2000 international units (IUs)/day and selegiline placebo; selegiline 10 mg/day and tocopherol placebo; or both active drugs.<sup>63</sup> The study demonstrated that selegiline delays the need to initiate levodopa therapy, likely due to symptomatic benefit rather than a neuroprotective effect. Although it has been shown to have the potential to modify the

disease, the major drawback to selegiline is that it is metabolized to potentially toxic amphetamine antibodies.<sup>60</sup>

Rasagiline, a second-generation MAO-B inhibitor, is not metabolized to amphetamine-like compounds. It has been found to be effective as monotherapy in early-stage PD without worsening insomnia. Rasagiline may also be utilized in combination with levodopa in patients with moderate or advanced PD, starting at 0.5 mg/day and increasing to 1 mg/day if necessary.<sup>60</sup>

A randomized, double-blind, placebo-controlled clinical trial of 404 patients with early PD demonstrated that rasagiline (at a dosage of 1 or 2 mg/day) improved UPDRS scores compared with placebo over a 26-week treatment period.<sup>65</sup> In the study's second phase, the placebo group was switched to receive rasagiline 2 mg/day for 6 months, while the other two groups continued receiving rasagiline 1 mg/day or 2 mg/day.<sup>66</sup> Follow-up at 12 months revealed that the group taking rasagiline the entire year showed less significant decline than did those in the delayed-treatment group (according to UPDRS scores).

Adverse events associated with rasagiline include headache, insomnia, xerostomia, abdominal discomfort, nausea, diarrhea, postural hypotension, dyskinesias, arthralgia, weight loss, anorexia, depression, vomiting, balance difficulty, and hallucinations.<sup>60</sup> A number of drugs are contraindicated for use with MAO-B inhibitors, and patients who receive treatment with rasagiline are advised to avoid foods that contain high concentrations of tyramine.

## Nonpharmacological Treatment Options

### Deep Brain Stimulation (DBS)

DBS is a surgical procedure used to treat the tremor, rigidity, stiffness, slowed movement, and walking problems associated with PD as well as ET.<sup>67</sup> DBS uses a surgically implanted, battery-operated neurostimulator (similar to a heart pacemaker and approximately the size of a stopwatch) to deliver electrical stimulation to targeted areas in the brain that control movement, blocking the abnormal nerve signals that cause tremor and PD symptoms. Currently, DBS is used only in patients for whom medication does not adequately control symptoms.

### Physical and Occupational Therapy

Physical therapy can improve independence and QOL in PD patients by improving movement, enhancing function, and minimizing pain.<sup>68</sup> Specifically, physical therapy can address a range of issues associated with PD, such as balance problems, lack of coordination, fatigue, gait, immobility, and weakness. Physical therapy can also help PD patients in the early stages in the disease establish an exercise program before motor symptoms appear.

The purpose of occupational therapy is to help PD patients perform the everyday activities that the disease impacts.<sup>68</sup> Occupational therapy assesses, treats, and recommends improvements in the following areas:

- Arm and hand therapy
- Handwriting aids
- Home modification
- Driver evaluation and vehicle modification
- Cooking and homemaking adaptations
- Eating and dinnerware adaptations
- Ways to maximize energy

- Computer modifications
- Workplace or work equipment modifications
- Leisure skill development
- Manual or electric wheelchair use
- Bathtub and toilet equipment use
- Dressing and grooming aids

## Summary

Challenges in diagnosing PD, specifically in recognizing non-motor symptoms of the disease, emphasize the need for better awareness of techniques for diagnosing and monitoring disease progression. Symptom-based criteria provide effective scales for monitoring treatment of PD, but evaluation of HRQOL should be included in the definition of treatment success. Emerging disease-modifying therapies may provide improved long-term outcomes and increased treatment success for PD patients. However, until reliable disease-specific biomarkers are found that enable the development of neuroprotective therapies, effective management of motor and nonmotor symptoms of PD through an individualized, patient-focused perspective is necessary to minimize disability, enhance HRQOL, and optimize treatment.

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