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# Parkinson disease: Managing a complex, progressive disease at all stages

## ■ ABSTRACT

Parkinson disease is a complex neurodegenerative disease with both motor and nonmotor symptoms. Levodopa remains the mainstay of therapy but is associated with motor complications as the disease progresses. A levodopa-sparing strategy may reduce or delay the onset of motor complications. New medical and surgical therapies offer improved control of motor complications in advancing disease. Recognition and treatment of nonmotor symptoms can improve quality of life throughout the course of the disease.

## ■ KEY POINTS

Although mild gait problems may be noted early on, significant difficulties with gait tend to emerge later, as the disease advances. In fact, early postural instability, gait problems, and falls suggest an alternative diagnosis.

The onset of symptoms at an earlier age is associated with earlier and more disabling motor fluctuations and dyskinesia and is a potentially important consideration when selecting initial medications.

Nonmotor symptoms are often overlooked but for some patients cause more disability than motor symptoms.

Depression should be diagnosed and treated, as it can lead to a decline in quality of life regardless of the degree of motor impairment. Selective serotonin reuptake inhibitors and tricyclic antidepressants can be used, although further clinical studies are needed to define their efficacy.

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**P**ARKINSON DISEASE IS COMPLEX to manage. Its presentation can vary, as can the response to treatment. Physicians tend to focus on its motor symptoms, but many patients find nonmotor symptoms equally troublesome. Levodopa is still the mainstay of therapy, but as the disease progresses, levodopa is associated with motor complications. More therapeutic options are available to manage these motor complications, and they offer hope but also add to the complexity for the clinician.

Internists and medical specialists other than neurologists will become increasingly involved in the care of patients with Parkinson disease, given our aging population and better recognition of this disease. This review summarizes the key features of Parkinson disease and its treatment.

## ■ NOT ONLY A DISEASE OF THE ELDERLY

Parkinson disease is common, being diagnosed in about 20 of every 100,000 people per year.<sup>1</sup> Although we often think of it as a disease of the elderly (the prevalence is about 1% in people over age 60 and 2% in those over age 80),<sup>2</sup> it can affect any age group; in fact, the mean age at onset is just under 60 years.

Patients share cardinal motor features but may display some differences in pathology, genetics, presenting motor features, and response to treatment.<sup>3,4</sup> Therefore, Parkinson disease may actually be a syndrome or a group of diseases with a variety of causes rather than a single disease.

## ■ WIDESPREAD CHANGES IN THE BRAIN

Parkinson disease is a chronic and progressive neurodegenerative disorder. It is characterized

TABLE 1

**Motor symptoms of Parkinson disease****Primary**

Akinesia and bradykinesia  
Rigidity  
Tremor  
Gait problems and postural instability (late finding)

**Other motor symptoms**

Dysphagia  
Sialorrhea secondary to decreased swallowing  
Hypophonia  
Micrographia  
Hypomimia (reduced facial expression)  
Motor initiation problems and freezing  
Dystonia (sustained involuntary contracture of muscle leading to pulling, twisting, or flexion at a joint)

**Motor complications****Motor fluctuations**

End-of-dose wearing-off  
Random fluctuations  
Lack of response to individual levodopa dose  
Early morning foot dystonia

**Dyskinesia: defined as peak dose or diphasic**

(at time of medicine absorption and wearing-off)  
Choreoathetoid  
Dystonic

pathologically by loss of pigmented nerve cells in the substantia nigra and by intraneuronal inclusions or Lewy bodies associated with neuronal damage.<sup>5</sup> The loss of nigrostriatal dopaminergic nerve cells and the disruption of cortical pathways in the basal ganglia are thought to contribute to the motor features or cardinal signs of Parkinson disease, namely bradykinesia, muscle rigidity, tremor, and, in part, postural instability.<sup>6</sup>

However, pathologic changes are more widespread. Nerve cell loss and Lewy body inclusions are also found in many sites distal to the nigrostriatal system, including the cortex, thalamus, hypothalamus, olfactory bulb, and brain stem. Alterations within the autonomic system extend from the hypothalamus and brain stem to the intermediolateral cell column of the spinal cord, sympathetic ganglia, and myenteric plexus in the gastrointestinal tract.<sup>5,7</sup>

Given these widespread changes, it is no wonder that additional, nonmotor symptoms

such as sensory, autonomic, and cognitive-behavioral problems occur, and that these respond poorly to dopaminergic therapy.

**WHO IS AT RISK?**

Although the etiology of Parkinson disease is still unclear, it is thought to involve a complex interaction between environmental exposure and genetics. Of the environmental influences that have been identified, the evidence is strongest for an increased risk in people exposed to pesticides.<sup>8</sup> Lifestyle factors also seem to affect risk<sup>9</sup>: lower risk has been noted in people who smoke,<sup>10</sup> use caffeine,<sup>11</sup> and exercise.<sup>12</sup>

**Is Parkinson disease familial?**

Many patients ask if their family members are at risk of developing the disease. Indeed, Rocco et al<sup>13</sup> reported a modest risk (relative risk 1.71) in first-degree relatives of patients with Parkinson disease evaluated in a clinic specializing in movement disorders. Furthermore, family studies have identified multiple genetic abnormalities with both dominant and recessive inheritance patterns.<sup>4</sup>

However, most Parkinson patients seen in an outpatient clinic do not have familial disease, and inherited forms are thought to account for only a small percentage of cases. Genetic abnormalities are thought to play a greater role in patients whose symptoms appear before 50 years of age.<sup>14</sup>

**DIAGNOSIS IS CLINICAL**

As yet, there is no objective test for Parkinson disease that is acceptably sensitive and specific early in its course, so the diagnosis is based on the clinical history and physical examination.

**Cardinal features**

The cardinal features include tremor at rest, rigidity, bradykinesia, and postural instability.<sup>15</sup> Gelb et al<sup>16</sup> have proposed that the diagnostic criteria include the presence of bradykinesia and rigidity or tremor.<sup>16</sup>

The motor symptoms of Parkinson disease (TABLE 1) usually begin unilaterally and progress slowly.

**Tremor**, the most easily recognized symptom, is present in 70% to 80% of patients.

Most patients have a tremor of 3 to 5 Hz at rest that improves when they move the affected body part. The tremor is often asymmetric and typically appears in the arm, leg, or chin. In contrast, essential tremor, for which parkinsonian tremor is often misdiagnosed, is faster (7 to 14 Hz), occurs with action or while holding a posture,<sup>17</sup> tends to begin more symmetrically, and is noted mostly in the hands or arms and the head or voice.

**Rigidity** is defined as a velocity-independent increase in tone. It may have a “cog-wheel” quality on examination—ie, when moved passively, the patient’s limb may seem to repeatedly catch and release.

Bradykinesia is a slowness in movement manifested by a decrease in movements such as spontaneous body gestures and in facial expression, and by difficulty with initiating movements or with performing sequential movements.

#### Other features

Additional findings at first evaluation can include loss of smell, difficulty getting out of a chair, micrographia (small handwriting), and a mask-like facial expression. Characteristic gait problems include flexed posture, decreased arm swing, and shortened stride, especially on the side that is more affected.

#### Features that suggest another diagnosis

Mild gait problems can arise early in the disease but become significant only as the disease advances. In fact, early postural instability, gait problems, and falls suggest another diagnosis.

Other features that suggest an alternative diagnosis include rapid progression, early autonomic dysfunction (orthostatic hypotension, sexual dysfunction, neurogenic bladder), symmetry of symptoms at onset, and lack of tremor.

#### Atypical forms of parkinsonism

Less common forms of parkinsonism include drug-induced parkinsonism, multisystem atrophy, progressive supranuclear palsy, vascular parkinsonism, and normal-pressure hydrocephalus.

Drug-induced parkinsonism (TABLE 2) is most often caused by dopamine-blocking

**TABLE 2**

### Drugs that can worsen motor symptoms of Parkinson disease

#### Typical antipsychotics

Chlorpromazine (Thorazine), fluphenazine (Prolixin), haloperidol (Haldol), thioridazine (Mellaril), trifluoperazine (Stelazine)

#### Atypical antipsychotics

Aripiprazole (Abilify), olanzapine (Zyprexa), risperidone (Risperdal), ziprasidone (Geodon)

#### Antiemetics

Metoclopramide (Reglan), prochlorperazine (Compazine, Compro), promethazine (eg, Phenergan)

#### Dopamine-depleting agents

Alpha-methyldopa (Aldochlor, Aldoril), methyldopa (Aldomet), reserpine (Serpalan, Serpasil), tetrabenazine (Nitoman, not available in the United States)

agents such as antipsychotics and antiemetics.<sup>18</sup> These drugs should also be avoided in patients with Parkinson disease, as they can worsen motor symptoms. Although the typical antipsychotics are most often implicated, the newer atypical agents also can cause parkinsonism, especially at higher doses.<sup>19</sup>

The differential diagnosis of atypical parkinsonism is well outlined in the literature, including reviews by Adler,<sup>20</sup> by Christine and Aminoff,<sup>21</sup> and the American Academy of Neurology Practice Parameter.<sup>22</sup>

#### ■ SYMPTOMS PROGRESS SLOWLY

The symptoms of Parkinson disease progress slowly over many years.<sup>23</sup> An abrupt decline or exacerbation of symptoms calls for an alternative explanation for the change, such as a recent change in medication, another illness such as infection, metabolic abnormality, dehydration, or significant physical or emotional stress.

Motor symptoms that contribute significantly to disability include motor fluctuations and dyskinesia (which are complications of levodopa treatment and are discussed further below), postural instability, problems with initiating movements (ie, motor initiation), and problems in speech and swallowing.

Postural instability is the inability to incorporate normal postural righting reflexes

**Given the prominent motor features, nonmotor symptoms are easy to overlook**

in response to perturbations of the center of gravity. One example of postural instability is retropulsion or the tendency to fall backwards, often without warning.

Motor initiation problems include an abrupt halt in all movement (“freezing”) when starting to walk, when changing direction while walking, and when walking in or through small, crowded spaces, such as door thresholds.

Speech changes most often include a hypophonic dysarthria characterized by a decrease in speech volume.

Adjusted for age, the overall risk of death is 2.7 times higher in nondemented Parkinson patients than in nondemented people in the same community.<sup>24</sup>

#### ■ NONMOTOR SYMPTOMS ARE COMMON AND TROUBLESOME

Because the motor features of Parkinson disease are so obvious, its many nonmotor symptoms are easy to overlook. However, nonmotor symptoms are common and troublesome and for some patients cause more disability than motor symptoms.<sup>25,26</sup> Up to 60% of patients suffer from more than one nonmotor symptom,<sup>27</sup> which can be autonomic, psychiatric, or sensory.<sup>28</sup>

##### Autonomic symptoms

The most common autonomic symptoms include orthostatic hypotension, impotence, urinary frequency and urgency, gastrointestinal motility problems with delayed gastric emptying and constipation, and thermoregulation, often experienced as a cold limb or drenching sweats.

##### Psychiatric symptoms

Cognitive and behavioral problems include sleep disorders, executive dysfunction, dementia, depression, anxiety, apathy, drug-induced psychosis, and disorders of impulse control. Depression, dementia, and medication-induced psychosis deserve special mention, as they are common and treatable and can lead to worsened quality of life, disability, and nursing home placement.<sup>29</sup>

**Dementia** may develop in more than 40% of patients.<sup>30</sup> Patients at higher risk of demen-

tia are older at disease onset, have a family history of dementia, or have bradykinesia and rigidity as the first symptoms.<sup>22</sup>

The onset of dementia occurs well into the course of Parkinson disease, which differentiates it from dementia with Lewy bodies, in which the onset occurs before or with the onset of parkinsonian motor symptoms.<sup>31</sup>

The acetylcholinesterase inhibitor rivastigmine (Exelon) modestly improves the cognitive and behavioral problems associated with dementia in both Parkinson disease with dementia and Lewy body disease.<sup>32,33</sup> Nausea, vomiting, and worsening tremor are the most common side effects.

Medication-induced visual hallucinations can be a problem in patients with dementia or in those who are taking a high dose of dopaminergic drugs. Clozapine (Clozaril) and quetiapine (Seroquel) are effective treatments if hallucinations persist despite medication adjustment.<sup>34</sup>

**Depression.** As many as 50% of patients with Parkinson disease have depression, yet it is often overlooked. It is important to recognize and treat it, as it can lead to a decline in quality of life regardless of the degree of motor impairment.<sup>35</sup>

Selective serotonin reuptake inhibitors and tricyclic antidepressants are used to treat depression in Parkinson disease,<sup>36</sup> although clinical studies are needed to further define their efficacy.<sup>37</sup>

##### Sensory symptoms

Common sensory symptoms include muscle or limb pain on the affected side, paresthesia, and restless leg syndrome.

#### ■ A TEAM APPROACH IS BEST

Nonpharmacologic treatment of Parkinson disease includes rehabilitation strategies aimed at improving daily function and quality of life, such as physical therapy, occupational therapy, speech and swallowing therapy, counseling, and social services. Rehabilitation therapies can be effective at all stages, from diagnosis to end-stage disease.

An interdisciplinary team approach shifts the focus beyond mobility and motor control and includes health promotion (safety, com-

**Dementia tends to arise later in Parkinson disease than in Lewy body dementia**

TABLE 3

**Current drug therapy for Parkinson disease****DOPAMINERGIC AGENTS****Initial therapy**

Carbidopa and levodopa (eg, Sinemet)  
 Dopaminergic agonist: ropinirole (Requip), pramipexole (Mirapex)  
 Monoamine oxidase B inhibitor: selegiline (Eldepryl, Zelapar),  
 rasagiline (Azilect)  
 Amantadine (Symmetrel)

**For advanced disease**

For motor fluctuations:  
 Catechol-O-methyltransferase inhibitor: entacapone  
 (Comtan or Stalevo), tolcapone (Tasmar)  
 Monoamine oxidase B inhibitor: selegiline, rasagiline (Azilect)  
 Dopaminergic agonists: ropinirole, pramipexole  
 "Rescue" therapy: apomorphine (Apokyn)

**For dyskinesia:**

Amantadine

**For motor fluctuations, tremor, and dyskinesia:**

Pallidal and subthalamic deep brain stimulation

**ANTICHOLINERGIC AGENTS**

Benzotropine (Cogentin)  
 Biperiden (Akineton)  
 Ethopropazine (Parsidol, Parsitan)  
 Trihexyphenidyl (Artane, Trihexane)

fort, and reduction of skin breakdown and other comorbidities), disease management (symptom recognition, prevention, or management), social support (including communication, caregiver training), and occupational therapy.<sup>38,39</sup>

### ■ INITIAL TREATMENT OF MOTOR SYMPTOMS

Drug treatment varies for different stages of Parkinson disease (TABLE 3). Drug treatment should begin when motor symptoms cause functional disability. Currently, initial therapy includes levodopa, dopaminergic agonists, monoamine oxidase B (MAO B) inhibitors, and amantadine (Symmetrel).

**Levodopa**

Levodopa is the mainstay of therapy for Parkinson disease and can improve all motor

symptoms in early disease. However, motor complications of levodopa therapy can occur as early as 2 years into therapy,<sup>40</sup> and 40% of patients experience these complications after 4 to 5 years of levodopa therapy.<sup>41</sup> These can be divided into two broad categories: motor fluctuations and dyskinesia.

**Motor fluctuations**, or reemerging parkinsonian symptoms, manifest first as an end-of-dose wearing-off of treatment effect. Over time, these fluctuations can change from a predictable end-of-dose phenomenon to a more randomly occurring fluctuation. The time during which a drug is effective and controls motor symptoms is often called the "on-time." Conversely, the "off-time" is the period when the drug's effectiveness wears off or when there is no effect.

**Dyskinesia**, or uncontrolled involuntary movements, occurs in up to 40% of patients after 5 years of levodopa therapy.<sup>41</sup> These movements can be either choreoathetoid or dystonic and most commonly represent a peak-dose effect.

These complications may be partially due to progression of the disease. As more dopaminergic cells are lost, there is a decreased capacity for cells to take up levodopa and store dopamine for continuous release. But levodopa has a short half-life (about 90 minutes), so the receptors are stimulated in pulses, with peaks and troughs in the drug's activity.<sup>42</sup>

Treatment of motor fluctuations requires more frequent dosing or the use of adjuvant agents, as described below. However, any increase in medication can be associated with and limited by dyskinesia.

**Strategies to reduce or delay levodopa's long-term complications** have been developed.<sup>43</sup>

In general, the onset of Parkinson disease at a younger age is associated with earlier and more severe motor fluctuations and dyskinesia.<sup>3</sup> This trend can be important to consider when selecting the initial medications.

A "levodopa-sparing" strategy, ie, starting with a dopaminergic agent with a longer half-life,<sup>44</sup> may delay the onset of motor complications. Amantadine, MAO B inhibitors, and dopaminergic agonists can be used as part of this strategy.

## Dopaminergic agonists

The dopaminergic agonists ropinirole (Requip) and pramipexole (Mirapex) effectively treat motor symptoms when used as initial monotherapy and may delay the onset of motor complications.

Two controlled trials<sup>45,46</sup> compared early treatment with levodopa, ropinirole, or pramipexole, with the primary outcome being the time to onset of motor complications. The dopaminergic agonists were titrated to an effective dose, and open-label addition of levodopa was allowed in all treatment groups to optimize motor function if needed. The incidence of end-of-dose wearing-off at 4 years was 47% in the pramipexole group and 63% in the levodopa group, and dyskinesia was noted in 25% of those taking pramipexole vs 54% of those taking levodopa. Similarly, the probability of developing dyskinesia at 5 years was lower in the ropinirole group than in the levodopa group (20% vs 45%).

These studies indicate that early use of dopaminergic agonists may reduce or delay the motor complications seen with levodopa use and should be considered as initial treatment, especially in patients at higher risk of developing these long-term complications.

Bromocriptine (Parlodel) and pergolide (Permax) are ergot-derived dopaminergic agonists. They have been used less often since they carry the risk of pulmonary and retroperitoneal fibrosis. Recently, concerns over heart valve damage with pergolide<sup>47,48</sup> led to its withdrawal from the market. Screening echocardiography may be considered in patients who have taken pergolide.

## Monoamine oxidase B inhibitors

The MAO B inhibitors selegiline (Eldepryl) and rasagiline (Azilect) are effective as initial monotherapy.<sup>49,50</sup> Selegiline is metabolized to an amphetamine and so should be used with caution in the elderly or in patients prone to anxiety, cognitive difficulties, or insomnia. Zylepar (Zydis selegiline—"Zydis" is the proprietary vehicle contained in this formulation) is a rapidly disintegrating tablet that minimizes first-pass metabolism, resulting in less amphetamine.<sup>51</sup>

## Amantadine

Amantadine, an antiviral agent and N-methyl-D-aspartate glutamate receptor antag-

onist, can be used to treat early symptoms. It is renally excreted, so it should be used with caution in older patients with reduced renal clearance. Other side effects are leg swelling, live-do reticularis, and cognitive problems.

## Other considerations when starting therapy

Side effects, cost, and long-term risk of motor complications should be considered when choosing an initial therapy. In general, dopaminergic agonists are more expensive than levodopa, have a higher risk of cognitive-behavioral side effects, and should be used with caution in the elderly or in patients with cognitive difficulties. Dopamine agonists are better tolerated in younger patients and should be considered as initial therapy in this group, which is also at greater risk of significant motor complications.

Conversely, levodopa should be considered in patients with cognitive problems or in older patients, who are at a lower risk of significant motor complications.

The American Academy of Neurology supports the use of levodopa, selegiline, and dopaminergic agonists as initial therapy.<sup>52</sup> It has not yet been established whether other strategies such as early use of catechol-O-methyltransferase (COMT) inhibitors aimed at more continuous dopaminergic stimulation would also delay the onset of motor complications and be appropriate as initial therapy.

## ■ CONTROLLING MOTOR FLUCTUATIONS

Motor symptoms become more difficult to control as the disease progresses. Over time, control of motor fluctuations and dyskinesia becomes a primary treatment goal (TABLE 3).

Strategies to delay or reduce levodopa-associated complications include dividing the levodopa dose so that it is given more times throughout the day, using controlled-release levodopa formulations, and using a COMT inhibitor such as entacapone (Comtan) or tolcapone (Tasmar).

Entacapone inhibits the metabolism of levodopa, increasing its duration of effectiveness, seen as an increase in total daily on-time with levodopa of slightly more than 1 hour.<sup>53</sup> Patients with a limited response to entacapone may benefit from switching to tol-

**Depression occurs in up to half of Parkinson patients, yet is often overlooked**

capone with an increase in on-time.<sup>54</sup> However, tolcapone may cause hepatotoxicity, so its use requires monitoring of liver enzymes. Tolcapone's effect is evident within a few weeks, and it should be discontinued in 3 weeks if on-time does not increase.

Adding a dopaminergic agonist and MAO B inhibitor can also reduce off-time in patients already taking levodopa.<sup>55-57</sup>

For patients who continue to experience significant off-time despite optimization of their oral regimen, subcutaneous apomorphine (Apokyn) may be helpful. Its fast onset of action (within 10 minutes) allows this drug to be used on an as-needed basis or as "rescue" treatment, that is, to be given during motor off-time to enhance movement until the next dose of oral medication takes effect.<sup>58</sup> However, difficulties with self-administration during off-time, cost, orthostasis, and the risk of dyskinesia and hallucinations associated with this treatment limit its use.

#### Adjunctive role of amantadine

Dyskinesias often render control of motor off-time more difficult. The strategies already discussed can improve on-time but may increase dyskinesia, requiring a reduction of the levodopa dose when adjunctive therapy is added.

To date, amantadine is the only drug available that improves motor symptoms and, in some patients, reduces the severity of dyskinesia.<sup>59</sup>

#### Adding drugs adds risk

As Parkinson disease progresses, more drugs are added to the regimen to optimize motor control, increasing the risk of adverse effects. The most common adverse effects, seen with all dopaminergic agents, include nausea, vomiting, sedation, hypotension, leg edema, hallucinations, and confusion.

#### The last drug added is not necessarily the first to be stopped

Patients or physicians often discontinue the last drug added when more than one drug is used to treat motor symptoms and intolerable side effects occur. However, we must consider the relative contribution of the entire class of dopaminergic drugs a patient is taking and eliminate the drug most likely to contribute to

a particular side effect rather than automatically discontinue the drug that was added last.

In older patients with cognitive decline, simplification of a patient's drug regimen to levodopa monotherapy may be necessary to reduce confusion or hallucinations or both. It is also helpful to implement one change at a time, not only to identify the cause of any new problems but also to best identify the change that led to improvement.

#### ■ WHEN IS SURGERY INDICATED?

Parkinson patients whose symptoms respond well to levodopa but who still suffer from significant tremor, end-of-dose wearing-off, or dyskinesia are ideal candidates for deep brain stimulation. Response to levodopa is one of the best predictors of favorable outcome.<sup>60</sup>

Deep brain stimulation involves surgical implantation of wires to stimulate specific areas of the brain, with resulting modulation of abnormal patterns of neuronal activity. Stimulation of both the globus pallidus interna and subthalamic nucleus improves tremor, rigidity, bradykinesia, motor fluctuations, and dyskinesia in nondemented patients with advanced idiopathic Parkinson disease.<sup>61,62</sup>

In general, the symptoms that typically do not respond to levodopa in advanced disease (ie, speech problems, postural instability, motor freezing, and cognitive dysfunction) do not respond to deep brain stimulation and continue to worsen as the disease progresses.

Deep brain stimulation improves motor function about as much as the best medical therapy but with a longer on-time, making it an effective treatment for patients with fluctuations or those whose treatment is limited by dyskinesia. In a study of 49 patients who underwent deep brain stimulation, the patients continued to score about 50% better than at baseline on measures of motor function and activities of daily living 5 years after implantation.<sup>62</sup>

Adverse events can be related to the surgery, to stimulation, to device damage or malfunction, and to disease progression.<sup>62</sup> The most common adverse events associated with surgery include hemorrhage, infection, and confusion. Long-term problems related to surgical treatment or postsurgical medication

**Rehabilitation therapies are useful at all stages of Parkinson disease**

changes include depression or apathy, mild cognitive changes, impulsivity, and weight gain.

## ■ MANAGING DYSTONIA AND TREMOR

The treatments for tremor and dystonia are considered separately here, as these symptoms may respond to different treatment strategies.

### Tremor

A subgroup of patients with Parkinson disease have tremor as the main motor feature. This subgroup also includes patients with benign tremulous parkinsonism, in which additional motor symptoms are minimal and progression is mild.<sup>63</sup>

Resting tremor can respond to dopaminergic medications such as levodopa and dopaminergic agonists. But in some patients with tremor-predominant disease, dopaminergic agents—including high-dose levodopa—do not adequately control tremor.

Anticholinergics (TABLE 3), as monotherapy or added to dopaminergic therapy, can be effective but are often limited by cognitive side effects. They should be used with extreme caution in elderly patients, who are at greater risk of these effects, and there is need for continual review of cognitive function at subsequent visits in this vulnerable patient group. Patients whose tremor does not respond to drug treatment may be considered for surgical deep brain stimulation despite adequate control of other symptoms.

### Dystonia

Dystonia is a sustained muscular contraction leading to twisting, pulling, or abnormal posturing or positioning across a joint. It can be a presenting symptom, especially with young-onset disease, an off-time symptom such as early morning foot dystonia, or a form of dystonic dyskinesia associated with drug therapy. It can be painful and can lead to significant functional impairment.

Dystonia presenting as an off-time symptom is best treated by reducing total off-time as described above. Anticholinergic therapy and antispasmodic agents may be helpful in some patients, but adverse effects often limit their use. Intramuscular injection of botulinum toxin is helpful and should be consid-

ered if oral therapy is already optimized or is ineffective.<sup>64</sup>

Deep brain stimulation of the globus pallidus interna or the subthalamic nucleus can improve dystonia in Parkinson disease and should be considered if medical therapy is otherwise optimized and if there is either associated pain or significant negative impact on quality of life.

## ■ MANAGING END-STAGE PARKINSON DISEASE

Motor problems in advanced Parkinson disease are severe rigidity and bradykinesia, hypophonic dysarthria, dysphagia, postural instability, and motor initiation problems leading to difficulties with gait. Additional concerns include depression, cognitive dysfunction, dementia, and drug-induced hallucinations. Older age at onset, dementia, falls, hallucinations, and decreased response to dopaminergic therapy are predictors of nursing home placement.<sup>65,66</sup>

### Hallucinations

According to new practice guidelines,<sup>37</sup> treatment of hallucinations should be considered after a thorough search for contributing systemic illness and medication causes. As mentioned above, the atypical antipsychotics clozapine and quetiapine effectively treat hallucinations with little if any worsening of motor symptoms.<sup>34,67</sup>

### Cognitive dysfunction

The acetylcholinesterase inhibitors donepezil (Aricept) and rivastigmine (Exelon) modestly improve cognitive function and behavior in Parkinson patients with dementia but may worsen tremor.<sup>32,68</sup>

### Other problems

- **Dysphagia.** Swallowing assessment is important, with treatment aimed at reducing aspiration related to dysphagia.
- **Depression** is also important to identify and treat, given the significant effect of depression on quality of life.
- **Fractures.** Bone scans should be obtained, given the high risk of fracture from falls in Parkinson patients with osteoporosis.<sup>69</sup>

**Anticholinergics can relieve tremor, but use them with extreme caution in elderly patients**

- **Melanoma.** Melanoma may be more common in Parkinson disease; therefore, all of these patients should have periodic skin examinations.

### RESEARCHERS EXPLORE NEUROPROTECTIVE THERAPIES

Neuroprotection is a hypothetical treatment strategy intended to delay or slow disease progression and is a major focus of research. Such an approach would dramatically change the

way we care for patients with Parkinson disease.

Agents studied as potential neuroprotective therapies include vitamin E, coenzyme Q10, *N*-methyl-D-aspartate receptor antagonists, the glutamate inhibitor riluzole (Rilutek), dopaminergic agonists, MAO B inhibitors, anti-inflammatory agents, and exercise. Studies have had methodologic flaws, and this plus the lack of a direct biologic marker for disease progression makes these studies difficult to interpret. To date, however, no neuroprotective therapy has been identified.<sup>70</sup>

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