

## Parkinson's disease

# Therapeutic strategies to improve patient function and quality of life

Fabio Danisi, MD

Idiopathic Parkinson's disease (PD) is an age-related neurodegenerative disorder characterized by slowness, stiffness, resting tremor, gait impairment, and postural instability. Levodopa is the most potent pharmacologic agent for symptom management and is associated with an increase in quality of life and longevity for patients with PD, but chronic use causes motor complications. The availability of several newer types of agents—dopamine agonists, monoamine oxidase inhibitors, and catechol-O-methyltransferase inhibitors—gives physicians increased flexibility with regard to first-line therapy, adjunct therapy, and managing or reducing the frequency of motor complications and other side effects associated with chronic levodopa therapy.

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**W**ith the recent availability of a range of medication options, pharmacologic treatment of Parkinson's disease has become more complex. Compared with levodopa, one of the most effective antiparkinsonian agents,<sup>1</sup> newer agents offer more targeted treatment according to the patient's age and symptom status, as well as better management of motor complications. These agents, however, may not be as well tolerated in older persons as levodopa.

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This article reviews the pharmacologic management of PD using levodopa/carbidopa, dopamine receptor agonists, monoamine oxidase-B inhibitors, and catechol-O-methyltransferase inhibitors. A discussion of levodopa/carbidopa therapy outlines the dosing recommendations with regard to initial therapy and management of motor complications. Tables summarize the recommendations for pharmacologic dosing.

### Background

With proper treatment, PD is a slowly progressing disease. Cases that arise in persons under age 50 and that are tremor-predominant tend to be milder than cases that arise after age 50 and that are not tremor-predominant (eg, bradykinesia, rigidity, etc). PD is slightly

more common in men than in women. A slightly increased risk also is associated with rural living, drinking well water, and exposure to industrial toxicants. The development of dementia is the highest risk factor for shortened life.<sup>2</sup> Without treatment, the duration of PD correlates with increased disability and mortality.

### Pathophysiology

Parkinson's disease is a progressive neurodegenerative disorder whose cause remains unknown. The pathologic hallmark of PD is the loss of pigmented, dopaminergic neurons of the substantia nigra pars compacta, coupled with the presence of intracellular inclusion bodies known as Lewy bodies.

### Symptoms, signs, and diagnosis

Diagnosis is clinical and is based on the presence of slowness of movement (bradykinesia), poverty of movement (hypo- and akinesia), rigidity, rest tremor, and postural instability. Other symptoms, such as shuffling gait, muffled speech (hypophonia), expressionless stare (hypomimia), and drooling are derived from these cardinal symptoms. Patients with PD may also have cognitive dysfunction, psychiatric symptoms (eg, endogenous anxious depression), autonomic dysfunction, musculoskeletal deformities, sensory

symptoms, sleep disturbances, and dermatologic problems.

Rest tremor, especially if unilateral, is suggestive of PD. Action and/or postural tremor with minimal rest tremor, in the absence of bradykinesia or rigidity, is suggestive of essential tremor (benign essential or familial tremor), not PD.

**Movement disorders.** Although mild bradykinesia can be a nonspecific feature of aging, in PD it typically presents asymmetrically and there is fatigability in movements, which become slower as a task or activity continues. One easy-to-use gauge of fatigability involves asking the patient to tap together the index finger and thumb as rapidly as possible.

Rigidity is not a feature of normal aging, and rigidity that improves with antiparkinsonian medications is likely caused by PD. Poor gait and balance are frequent findings in older persons and are often multifactorial (eg, poor vision, sensory loss, cerebellar disease, stroke, bone and joint disease).

Postural instability is an infrequent presenting symptom in PD and should prompt investigation for other causes of parkinsonism. Cognitive, sleep, and autonomic problems all occur at a higher than normal rate in older patients with PD. Drug-induced parkinsonism (also known as secondary parkinsonism) occurs most often in older patients.<sup>3</sup>

### Pharmacologic treatment

Nonpharmacologic treatment—particularly patient education—is an important component of PD management and should not be overlooked. Olanow et al provide a helpful algorithm that addresses nonpharmacologic, pharmacologic, and surgical considerations in the management of PD.<sup>4</sup> The Worldwide Education and Awareness for Movement Disorders web site ([www.wemove.org](http://www.wemove.org)) offers information on PD for clinicians and patients.

**Symptomatic treatment.** Symptomatic intervention involves improving function using the lowest effective dose of

**Table 1** Dosing recommendations for Levodopa

Agent	Starting dose	Precautions
Carbidopa/levodopa* (Sinemet)	25/100 mg tid	Hypotension, nausea confusion, dyskinesia
Carbidopa/levodopa* (Sinemet CR)	25/100 mg tid	Same as above

\* First-line or add to dopamine agonist  
CR: Controlled release  
Source: Prepared for Geriatrics by Fabio Danisi, MD

medication.<sup>4</sup> Acceptable function is determined by the patient and may vary greatly depending on the patient's life circumstances. There is no benefit in delaying symptomatic therapy once the patient develops disability (eg, a mild tremor or gait disturbance that impedes the ability to perform key physical tasks). Symptomatic treatment of PD involves use of agents that:

- increase dopamine levels (levodopa/carbidopa)
- stimulate dopamine receptors (dopamine receptor agonists)
- inhibit dopamine metabolism and reduce fluctuations in plasma levodopa levels (monoamine oxidase-B inhibitors [MAO-B]; catechol-O-methyltransferase [COMT] inhibitors)
- improve symptoms through non-dopaminergic mechanisms (antiviral, anticholinergics).

Levodopa/carbidopa and most dopamine agonists are appropriate first-line therapies. Each type can be prescribed as an adjunct to the other. Moreover, dopamine agonists are increasingly used in younger patients with PD (age < 70) as initial therapy, because they decrease the incidence of levodopa-induced motor complications.

The antiviral amantadine is appropriate second-line therapy for managing motor fluctuations and in some patients with early PD may be tolerated as monotherapy or as an adjunct to other agents.

The MAO-B inhibitors are indicated for use as adjunct therapy in patients taking levodopa, but they may also have a role in initial therapy and this potential continues to be investigated. The

COMT inhibitors can serve as adjunct therapy to lengthen levodopa half-life, particularly when patients start experiencing motor fluctuations (see "Levodopa complications" below). Anticholinergics can be used as second-line therapy to help manage tremors but also can cause confusion.

As a rule, start all medications at a very low dose, then increase the dose incrementally over several weeks (typically 4 to 6) until symptoms improve or intolerable side effects arise.<sup>5</sup>

If treatment is limited because of side effects, antiparkinsonian medications should be withdrawn. In patients taking multiple antiparkinsonian agents, withdraw the agents in reverse order of their known effectiveness (eg, withdraw anticholinergics first, amantadine second, MAO-B inhibitors third, dopamine agonists fourth, then levodopa). Once less effective agents are withdrawn, patients may tolerate higher doses of levodopa to control symptoms.

Patients who fail to respond to antiparkinsonian medications—particularly levodopa/carbidopa—may not have PD and should undergo further examination.

### Levodopa/carbidopa

Levodopa is always used in combination with carbidopa, thus the combination of levodopa/carbidopa is commonly referred to as levodopa. Carbidopa prevents decarboxylation of levodopa in the periphery and thus increases the amount of unmetabolized drug that can cross the blood-brain barrier. Carbidopa also reduces the side effects of levodopa.

*continued*

Compared with other antiparkinsonian agents, levodopa is the most effective and best tolerated. Levodopa use also is associated with an increase in quality of life and longevity for patients with PD.<sup>2</sup> Table 1 summarizes levodopa dosing recommendations.

Levodopa should be used as first-line therapy in all persons age 70 and older in whom PD develops because:

- the risk of developing levodopa-induced motor complications in this group is lower than it is in persons under age 70
- it is less likely to cause complications in the presence of concomitant illnesses and medications.

### Levodopa should be used as first-line treatment in all persons age 70 and older

Because it is better tolerated (ie, produces the fewest cognitive and behavioral side effects) than other antiparkinsonian agents, levodopa also should be used as initial therapy in all patients who present with cognitive impairment.

**Good response.** In general, patients with PD respond well to levodopa. In a study performed in the United Kingdom, 96% of patients who had autopsy-proven PD had a definite response to levodopa.<sup>6,7</sup>

In patients with early PD, treatment with levodopa (Sinemet), 25/100 mg tid, typically produces marked symptom improvement shortly after the regimen begins. The minimum dosage of carbidopa required for effective inhibition of the peripheral aromatic amino acid decarboxylase system is 75 mg/d.

**Optimal regimen elusive.** No studies have determined the optimal initial antiparkinsonian regimen for the older patient. In general, patients of all ages

with PD who are otherwise healthy and cognitively intact should avoid levodopa as initial therapy because of the risk of development of motor complications after a few years of treatment. In such patients, initial symptomatic therapy may include a dopamine agonist and/or the MAO-B inhibitor selegiline (Eldepryl).

When there is diagnostic uncertainty regarding an older patient with an akinetic-rigid syndrome, empirical levodopa therapy, 25/100 mg/d, is appropriate. The dose is slowly increased in stepwise fashion until symptoms improve or intolerable side effects emerge.

**Diet.** Patients taking levodopa should avoid high-protein meals or foods (eg, milk products, meat, fish, poultry) at the time of medication intake as amino acids from the diet compete with the drug for absorption through the gut. Ingestion should be avoided within 30 minutes before or after a meal. The recommended alternative is smaller, more frequent meals.

#### Levodopa complications

In approximately 50% of patients and after roughly 5 years of chronic levodopa therapy, the most common motor complications are motor fluctuations and dyskinesia (see below). Disease duration and cumulative levodopa dose are the best predictors of motor complications.<sup>8</sup>

In early PD, surviving nigral cells are sufficient in number to store exogenous dopamine presynaptically. As the disease progresses and the number of surviving nigral cells dwindles, this buffering capacity decreases, and the clinical response begins to coincide with the levodopa plasma half-life, which is approximately 90 minutes. Changes also occur at the dopamine receptors. Collectively these processes lead to motor complications.

Motor fluctuations are characterized by:

- transition from short periods of symptomatic control (“on”) typically lasting 1.5 to 4 hrs to re-emergence of

symptoms (“off”; end of dose “wearing off”) due to the short half-life of levodopa

- severe and unpredictable swings between “on” and “off”; hence the “on-off” or “yo-yo” phenomenon, caused by even minor fluctuations in levels of levodopa in the blood.

Dyskinesias are involuntary choreiform (dance-like) or dystonic (abnormal posturing) movements that typically arise at the peak of each levodopa dose. They typically occur in patients who have already developed motor fluctuations.

#### Managing motor complications

Several strategies can be used to reduce motor complications caused by levodopa therapy. They include:

- using smaller and more frequent dosing (in general, every 3 hours, but for patients with severe motor complications, up to every 2 hours)
- adding or increasing the dose of dopamine agonists
- increasing the half-life of levodopa with MAO-B or COMT inhibition
- adding the antiviral amantadine to reduce dyskinesia.

Controlled-release levodopa (Sinemet CR) does not appear to help reduce long-term levodopa-induced motor complications, although in select patients it is beneficial due to its longer half-life of approximately 3 hours. Compared with standard (immediate-release) levodopa, however, absorption of controlled-release levodopa is slower and less predictable. Thus onset of action is slower, and bioavailability is approximately 75% of an equivalently dosed immediate-release preparation. Controlled-release levodopa, 25/100 or 50/200 mg, is sometimes helpful when given as the last dose of the day, particularly for patients who suffer from sleep fragmentation or severe “offs” early in the morning.

Increasing the dose frequency and adding an adjunct agent can be done in short succession—one intervention enhances the other. If the patient does not appear likely to tolerate a dopamine

**Table 2** Dosing recommendations for dopamine agonists

Agent	Starting dose	Precautions
<b>Bromocriptine mesylate</b> (Parlodel)	2.5 mg tid	Hypotension, nausea, livedo reticularis, edema, confusion, hallucinations
<b>Pergolide mesylate</b> (Permax)	0.05 to 0.25 mg tid	Same as above
<b>Pramipexole</b> (Mirapex)	0.125 mg tid	Nausea, hypotension, sedation, hallucinations
<b>Ropinirole HCl</b> (Requip)	0.25 mg tid	Nausea, hypotension, sedation, hallucinations

Source: Prepared for Geriatrics by Fabio Danisi, MD

agonist because of cognitive issues, consider COMT inhibition.

### Dopamine agonists

Compared with levodopa, dopamine agonists have a longer half-life and do not induce significant wearing off or dyskinesia. Dopamine agonists are generally well-tolerated as initial monotherapy in early PD. Starting patients with early PD on dopamine agonist monotherapy or a dopamine agonist in combination with levodopa delays the onset and reduces the severity of motor complications compared with starting them on levodopa alone.<sup>9,10</sup> Cognitive side effects are more frequent in patients treated with dopamine agonists compared with those treated with levodopa. In advanced PD, dopamine agonists reduce the severity of motor complications.

Use of dopamine agonists is limited by their side-effect profile: nausea, orthostatic hypotension, drowsiness, hallucinations, and confusion. Inevitably, advanced PD patients on dopamine agonist monotherapy will require the addition of levodopa. Table 2 summarizes dopamine agonist dosing recommendations.

### Antiviral

Amantadine (Symmetrel) is an antiviral agent with antiparkinsonian properties. It increases dopamine release, blocks dopamine reuptake, and may block N-methyl-D-aspartate glutamate receptors. Amantadine is sometimes useful in early-onset PD. It has been

found particularly useful to treat levodopa-induced dyskinesia. Its use is limited, however, by its side-effect profile, particularly cognitive impairment. Thus it is rarely used in older patients.

### COMT inhibitors

A COMT inhibitor is always used in combination with levodopa.<sup>11</sup> By blocking the 3-O-methylation of levodopa, these agents prolong the action of each levodopa dose and thereby reduce "off" durations. Table 3 summarizes COMT-inhibitor dosing recommendations.

Entacapone (Comtan) is indicated as an adjunct to levodopa to treat patients with idiopathic PD who experience the signs and symptoms of end-of-dose wearing off. The agent blocks COMT peripherally and has a shorter half-life than tolcapone (see below). It is administered concomitantly with each levodopa/carbidopa dose, up to a maximum of 8 times daily.

Entacapone has not been associated

with severe liver toxicity or other life-threatening effects. Urine discoloration, nausea, and increased dyskinesia are the most frequent side effects. Slightly reducing the dose of levodopa can treat dyskinesia.

The COMT inhibitor tolcapone (Tasmar) also prolongs levodopa half-life without increasing the peak levodopa plasma concentration. It is more potent than entacapone and can be given tid. Upon initiating tolcapone, the levodopa dose should be reduced by approximately 30%.

In 2000, the Food and Drug Administration issued a black box warning regarding a potential association between liver toxicity and tolcapone use. Three deaths from liver toxicity have been described in patients taking tolcapone in Europe.<sup>12</sup> The FDA mandates obtaining informed consent before starting tolcapone and liver function monitoring every 2 weeks for the first year and less frequently thereafter. Common side effects of tolcapone include dyskinesias, nausea, sleep disorders, and muscle cramps.

Despite the precautions, tolcapone is an effective antiparkinsonian agent, provided the physician exercises prudence in dosing and closely monitors patient status.

### MAO-B inhibitors

Monoamine oxidase inhibitors are irreversible inhibitors of monoamine oxidase. Selegiline HCl (Eldepryl) is indicated as an adjunct in the management of Parkinson's patients in

**Table 3** Dosing recommendations for COMT inhibitors

Agent	Starting dose	Precautions
<b>Entacapone*</b> (Comtan)	200 mg with each dose of levodopa (maximum 8 tabs or 1,600 mg/d)	Urine discoloration (benign), diarrhea
<b>Tolcapone†</b> (Tasmar)	100 mg tid	Same as entacapone, plus hepatotoxicity (liver monitoring required)

\* Add to levodopa; second-line therapy for wearing-off symptoms

† Add to levodopa; third-line therapy for motor fluctuations

Source: Prepared for Geriatrics by Fabio Danisi, MD

whom levodopa therapy loses effectiveness.

Selegiline blocks the oxidative deamination of dopamine and increases dopamine half-life in the brain. It is partially metabolized to amphetamines. It is taken every morning or twice per day; the second dose should always be taken before noon to prevent insomnia. Dosing increases should be avoided.

By blocking monamine oxidase, selegiline is thought to inhibit the transformation of dopamine to oxygen free radicals. No evidence, however, shows that selegiline offers neuroprotection in humans. It produces mild symptomatic side effects and has been shown to delay the need for initiation of levodopa therapy by approximately 9 months.<sup>13</sup>

In contrast to dopamine agonists, no data support the use of selegiline for initial monotherapy. Given its putative neuroprotective effects, however, some clinicians use selegiline to manage early PD. In more advanced PD, selegiline improves motor fluctuations in one-half to two-thirds of patients. Whether selegiline alone or in combination with other antiparkinsonian medications affects mortality remains unanswered.<sup>14,15</sup>

## Anticholinergics


Because of their potential for cognitive and other undesirable side effects, anti-cholinergics are rarely used in older patients with PD. They are most effective for management of tremor, although in general PD tremor is not disabling, given that it is typically present only at rest and subsides with action.

## Conclusion

The availability of numerous anti-parkinsonian agents makes pharmacologic management of PD challenging, but also offers clinicians flexibility in creating treatment regimens and dealing with motor complications resulting from initial therapy. Levodopa is recommended for first-line therapy in patients whose symptoms emerge after

age 70; patients with PD who are otherwise healthy and cognitively intact should avoid initial therapy with levodopa. In younger patients diagnosed with PD symptoms, dopamine agonists are effective for initial therapy. COMT-inhibitors, dopamine agonists, and, in select cases selegiline or amantadine, are effective and appropriate adjunct treatments for patients who develop motor complications on initial therapy.

Although commonly overlooked as part of treatment of PD, nonpharmacologic considerations—patient education, exercise, and diet—play a key role in improving quality of life and helping manage symptoms. Thus non-pharmacologic intervention should be part of the treatment regimen. Depression, dementia and psychosis, and sleep hygiene also are important considerations for effective management of PD.

Patients who develop motor complications and those with cognitive, autonomic or other neurologic symptoms should be referred to a neurologist, preferably at a Parkinson's disease referral center. 

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**Danisi F. Parkinson's disease: Therapeutic strategies to improve patient function and quality of life. Geriatrics 2002; 57(March):46-50.**

1. A catechol-O-methyltransferase (COMT) inhibitor is always used in combination with:
  - a. monoamine oxidase inhibitors
  - b. levodopa
  - c. selegiline
  - d. entacapone
2. Selegiline blocks the oxidative deamination of dopamine and increases the half-life of what in the brain:
  - a. serotonin
  - b. acetylcholine
  - c. C-reactive protein
  - d. dopamine
3. For management of Parkinson's disease (PD), levodopa should be used as first-line therapy in all persons:
  - a. exhibiting motor complications
  - b. under age 70
  - c. age 70 and older
  - d. none of the above
4. Common strategies for managing motor complications include:
  - a. using larger and more frequent dosing
  - b. decreasing the dose of dopamine agonists
  - c. increasing the half-life of carbidopa with MAO-B or COMT inhibition
  - d. none of the above
5. Motor complications from levodopa therapy include motor fluctuations and dyskinesia.
  - a. True
  - b. False
6. Patients who fail to respond to antiparkinsonian medications—particularly levodopa/carbidopa—may not have:
  - a. health insurance
  - b. PD
  - c. dementia
  - d. motor fluctuations
7. Patients taking levodopa should avoid what at the time of medication intake:
  - a. family members
  - b. carbohydrates
  - c. high-protein meals or foods
  - d. eye contact with caregivers
8. Diagnosis of PD is based in part on the presence of:
  - a. bradykinesia
  - b. hypo- and akinesia
  - c. rigidity, rest tremor, and postural instability
  - d. all of the above

**In addition to the exam questions, answer the following evaluation questions: (1=strongly agree, 6=strongly disagree)**

- |  |   |
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