



# Therapeutic Options

## FOCUS ON PARKINSON'S DISEASE

Parkinson's disease (PD) is a slowly, but relentlessly, progressive neurodegenerative disorder that leads to significant disability and impaired quality of life.<sup>1-3</sup> The prevalence of PD is about 0.3 per cent in the general population and 1–2 per cent in individuals older than 60 years.<sup>4</sup> The disorder becomes increasingly common with advancing age, and affects men more often than women.<sup>4,5</sup> Diagnosis typically occurs between the ages of 60 and 70 years (mean onset, 62.5 years).<sup>6</sup>

At present, there is no unequivocally proven way to slow or alter the course of PD, although many of the symptoms are responsive to drug therapy.<sup>6,7</sup> This article provides a brief overview of PD, with a focus on the pharmacological management of core motor symptoms and complications.

### PATHOGENESIS AND RISK FACTORS

The central pathology in PD is a loss of dopaminergic neurons in the substantia nigra pars compacta of the basal ganglia, resulting in decreased dopamine activity in nigrostriatal tracts (with a compensatory increase in acetylcholine activity).<sup>1,6,8</sup> The mechanisms

of cell death contributing to neuronal loss in PD are incompletely understood, but likely involve mitochondrial dysfunction, oxidative stress, altered protein handling, and inflammatory changes that lead to apoptosis or autophagy.<sup>9</sup> Although the presence of Lewy bodies is a defining feature of AD, their relevance to disease pathogenesis remains uncertain.<sup>9</sup>

Risk factors for PD identified in epidemiologic studies include advanced age (the most important risk factor), family history of PD, early-life rural living, and early exposure to pesticides.<sup>4,9</sup> Plant-derived toxins, bacterial and viral infection, and exposure to organic solvents, carbon monoxide, and carbon disulfide have also been identified as environmental factors influencing the occurrence of PD.<sup>9</sup> It is postulated that both genetic susceptibility and environmental factors play a role in PD development.<sup>4,6,9</sup>

### SYMPTOMATOLOGY AND PROGRESSION

The cardinal motor symptoms of idiopathic PD are summarized in Box 1. At presentation,

75 per cent of patients are affected unilaterally or asymmetrically; motor slowing may be limited to muscles of a single extremity.<sup>4,6</sup> However, problems become bilateral as the disease progresses.<sup>4,6</sup> In early PD, symptoms are mild, disability is minimal to mild, and there is no postural instability.<sup>2</sup> With progression, increasing signs of bradykinesia occur; patients often have a slow, shuffling gait, and stooped posture.<sup>4</sup> In more advanced stages, motor manifestations can include gait freezing (as if the patient's foot were stuck to the floor), postural instability, and falls.<sup>4,6</sup>

While it is motor symptoms that define the classic PD patient, nonmotor features (see Box 2) contribute substantially to disease burden and are often less responsive or unresponsive to traditional PD therapies.<sup>6,10</sup> Such nonmotor symptoms may occur early or late in the disease course, but are more common in advanced PD.<sup>4,11</sup>

### PHARMACOTHERAPY

An overview of the pharmacological management of motor manifestations of PD, and motor complications associated with levodopa therapy (see Box 3), is

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**Box 1 – Cardinal motor symptoms of Parkinson's disease<sup>3,4,6</sup>**

**Tremor at rest**

- May be subtle, involving only a thumb or a few fingers
- Usually one of the first symptoms to appear, but absent in 20 per cent of patients at presentation

**Bradykinesia**

- Characterized by slow initiation of voluntary movement, with a progressive reduction in speed and amplitude of sequential motor tasks

**Rigidity**

- Present upon passive movement of major joints

**Gait disturbance**

- Typically includes walking with small steps

**Box 2 – Some nonmotor features of Parkinson's disease<sup>4,6,11-13</sup>**

**Autonomic**

- Gastrointestinal symptoms (e.g., constipation, dysphagia, gastroparesis)
- Hypersalivation
- Orthostatic hypotension
- Sexual dysfunction (e.g., erectile dysfunction)
- Thermoregulatory dysfunction (e.g., heat/cold intolerance, excessive sweating)
- Urinary symptoms (e.g., incontinence, nocturia, urgency)

**Neuropsychiatric**

- Anxiety
- Cognitive impairment
- Dementia
- Depression
- Psychosis

**Sensory**

- Pain
- Paresthesias

**Sleep**

- Daytime somnolence
- Insomnia
- REM sleep behaviour disorder\*
- Restless legs syndrome

**Other**

- Dysarthria (trouble pronouncing words)
- Fatigue
- Hypophonia (soft speech)
- Masked facies (reduced facial expression)

\* A type of parasomnia characterized by patients acting out dramatic or violent dreams during the REM sleep stage.<sup>12</sup>

**Box 3 – Motor complications associated with levodopa\* 1,4,5,11**

**Motor fluctuations†**

Wearing-OFF/end-of-dose deterioration

- A generally predictable recurrence of symptoms that precede a scheduled levodopa dose; improvement usually occurs with dosing
- Related to progressive loss of presynaptic dopaminergic cell terminals, leading to a decrease in striatal dopamine storage capacity and subtherapeutic levodopa trough concentrations between doses
- The earliest and most common pattern of motor fluctuation

Delayed ON or dose failure/no ON

- Believed to result from impaired or delayed levodopa absorption in the proximal jejunum or across the blood–brain barrier

- Erratic or delayed gastric emptying and competition with dietary amino acids for uptake likely play a role

Unpredictable OFFs or random ON–OFF swings

- Fluctuations happen quickly, randomly, and seemingly unrelated to timing of last medication dosing
- Generally occur in advanced disease stages

**Dyskinesias‡**

ON-period dyskinesias

- Typically choreic or ballistic in nature; most frequently affect the limbs and trunk and appear first on the side of the body most afflicted by Parkinson's disease
- Predominantly dystonic if affecting the face or neck

- Most common at the time of peak drug levels, but can occur throughout the ON period

Biphasic dyskinesias

- Usually occur at the beginning and end of a dose interval (when levodopa levels are below a certain threshold level)
- Generally comprise a mix of phasic and dystonic movements
- Relatively uncommon

OFF-period dyskinesias

- Predominantly dystonic, often affecting the ankles/feet/toes; usually seen in the early morning and generally painful

\* Prevalence estimates for levodopa-induced motor complications vary (e.g., ~33 per cent by two years,<sup>1</sup> 40 per cent after four to six years,<sup>4</sup> 30–50 per cent by five years,<sup>4</sup> 70 per cent by three years in those with young-onset Parkinson's disease<sup>14</sup>). It is postulated that nonphysiological, pulsatile stimulation of dopamine receptors plays a key role in their development.<sup>1</sup>

† Patients with motor fluctuations alternate between being "ON" (good response to levodopa with good motor function) and "OFF" (levodopa effects absent with reappearance of motor symptoms; nonmotor symptoms such as anxiety, akathisia, confusion, and excessive sweating may also manifest during OFF periods).<sup>4,5,11</sup>

‡ Levodopa-induced dyskinesias cover a broad spectrum of involuntary jerky movements, slow dystonic movements, fixed dystonic postures or, more rarely, myoclonus or ballism.<sup>1,4,11</sup>

presented below. A discussion of the treatment of nonmotor features of PD is beyond the scope of this review; however, management recommendations are made in guidelines<sup>11,12</sup> available online (see References, below, for URLs).

A listing of drugs utilized for motor symptoms of PD, along with comments regarding their use, is provided in Table 1.

Medication selection for an individual patient will depend on several factors, including specific signs and symptoms and their effect on function and quality of life, age, and consideration of complications associated with long-term therapy.<sup>2,4</sup>

**Early disease: initiating therapy**

There is considerable debate about when and

how to initiate pharmacological therapy in PD.<sup>19</sup> Nonetheless, it is generally agreed that treatment be instituted before a patient experiences significant functional impairment.<sup>10,19</sup>

While there is consensus that levodopa is the most effective therapy for motor symptoms of PD (especially rigidity and bradykinesia), long-term levodopa treatment is associated

with the development of motor complications (see Box 3) that, once present, are difficult to manage and contribute significantly to overall disability and disease burden.<sup>1,2,4,6,7,10,15</sup>

Although drug therapy can be commenced with a variety of different agents (see Table 1), levodopa or a dopamine agonist are often recommended.<sup>6,7,10</sup> Dopamine agonists have been cited as the second-most effective class of drugs for motor symptoms of PD, although this assertion is not based on head-to-head trials.<sup>6,10</sup> Dopamine agonists carry a lower risk of motor complications than levodopa and may be recommended as initial therapy for younger patients (e.g., <60 years) who are more prone to developing such complications.<sup>6,7,10</sup> Early use of levodopa has been recommended for older patients.<sup>10</sup> Regardless of age, most experts agree that withholding levodopa should not be at the expense of good symptomatic control, which may itself be a predictor of favourable long-term outcomes.<sup>18</sup> The majority of evidence

suggests that, in the long term (6–10 or more years following treatment initiation), clinical measures of parkinsonism are generally equal in patients initially treated with either levodopa or a dopamine agonist.<sup>19</sup>

Monoamine oxidase inhibitors are also an option for early treatment of PD, but they are less effective than levodopa and tend to result in smaller symptom improvements than dopamine agonists.<sup>7,10</sup>

Anticholinergic agents have only small effects on most PD motor symptoms.<sup>10</sup> Although they are often cited as being particularly effective for tremor, rigorous supporting evidence is lacking.<sup>10</sup>

Amantadine has mild antiparkinsonian activity, and may be of limited value in early PD.<sup>4</sup>

**Advancing and advanced disease: modifying therapy**

As symptoms progress, adjustments to medication therapy are necessary. In patients

not initially started on levodopa or a dopamine agonist, the addition of one of these agents is warranted.<sup>10</sup> As for initial therapy, the choice between levodopa and an agonist will depend primarily on prioritization of symptom control (greater with levodopa) and avoidance of motor complications (less with agonists in the first 3–5 years) and neuropsychiatric events (e.g., hallucinations; greater with agonists).<sup>10,11</sup> It is notable that after five years of treatment, more than 80 per cent of patients will need levodopa to control PD symptoms.<sup>7</sup>

For patients started on dopamine agonist therapy, options include increasing the dopamine agonist dose, switching to another dopamine agonist, or adding levodopa.<sup>10</sup> For patients started on levodopa, options include increasing the dose of levodopa, adding a dopamine agonist, or adding a catechol-*O*-methyltransferase (COMT) inhibitor (when motor fluctuations evolve).<sup>10</sup>

Later-stage PD is inevitably associated

**Table 1 – Some medications for Parkinson's disease<sup>6-8,10,11,15-18</sup>**

Drug class/Drug	Comments
Levodopa (with a DDI*)	<ul style="list-style-type: none"> <li>• Converted to dopamine <i>in vivo</i>; administered with a DDI to prevent peripheral conversion to dopamine and resultant side effects (e.g., nausea, vomiting)</li> <li>• In early PD, usually dosed three times daily with good daytime symptom control</li> <li>• Use of CR levodopa in early PD has no significant preventive effect on incidence of motor complications compared with standard levodopa</li> <li>• CR and standard levodopa formulations result in similar symptom control</li> <li>• Commonly used with other antiparkinsonian medications to improve symptoms</li> <li>• Risk of levodopa-induced dyskinesias is dose-dependent</li> </ul>
<b>Dopamine agonists</b> <ul style="list-style-type: none"> <li>• Bromocriptine</li> <li>• Cabergoline</li> <li>• Pergolide†</li> <li>• Pramipexole</li> <li>• Ropinirole</li> </ul>	<ul style="list-style-type: none"> <li>• Most patients started on DA monotherapy will require levodopa (as replacement or adjunctive therapy) to control motor symptoms after a few years (&lt;20 per cent of patients remain on DA monotherapy after five years)</li> <li>• Available evidence reveals no major differences in efficacy among the DAs in early PD</li> <li>• Associated with a higher incidence of certain side effects (e.g., hallucinations, impulse-control disorders, somnolence, dizziness, leg edema) than levodopa</li> <li>• Ergot derivatives (bromocriptine, cabergoline, pergolide) are not recommended as first-line medications due to an increased risk of fibrotic reactions (e.g., lung, retroperitoneal, and heart valve fibrosis)</li> </ul>
<b>MAO-B inhibitors</b> <ul style="list-style-type: none"> <li>• Rasagiline</li> <li>• Selegiline</li> </ul>	<ul style="list-style-type: none"> <li>• Prevent the breakdown of dopamine, increasing dopamine availability; additional mechanisms may contribute to clinical effects</li> <li>• May reduce the rate of motor fluctuations compared with initial levodopa therapy</li> <li>• In contrast to selegiline, rasagiline is not metabolized to amphetamine and has no sympathomimetic activity</li> <li>• Easy to administer (once daily dosing, no titration) and well tolerated (especially rasagiline)</li> <li>• Selegiline doses should not exceed 10 mg/day to minimize risk of dietary tyramine-related interactions</li> </ul>
<b>COMT inhibitors</b> <ul style="list-style-type: none"> <li>• Entacapone</li> <li>• Tolcapone†</li> </ul>	<ul style="list-style-type: none"> <li>• Reduce the metabolism of levodopa, extending its plasma half-life and prolonging the action of each dose; as such, COMT inhibitors should always be given in combination with levodopa</li> <li>• Tolcapone is not a first-line medication due to an increased risk of hepatotoxicity (only recommended for patients failing all other medications)</li> </ul>
<b>Anticholinergics</b> <ul style="list-style-type: none"> <li>• Benztropine</li> <li>• Trihexyphenidyl</li> </ul>	<ul style="list-style-type: none"> <li>• Believed to act by correcting the disequilibrium between striatal dopamine and acetylcholine neurotransmission</li> <li>• Poorly tolerated in the elderly (associated with an increased risk of cognitive deterioration); usually reserved for young patients in whom tremor is a problem and response has been inadequate to other drugs</li> </ul>
Amantadine	<ul style="list-style-type: none"> <li>• Effects may be mediated by various mechanisms, including blockade of NMDA glutamate receptors, anticholinergic effects, and release of presynaptic dopamine stores</li> </ul>

COMT = catechol-*O*-methyltransferase; CR = controlled-release; DA = dopamine agonist; DDI = dopa-decarboxylase inhibitor; MAO-B = monoamine oxidase type B; NMDA = N-methyl-D-aspartate; PD = Parkinson's disease

\* In Canada, levodopa is available in combination with the dopa-decarboxylase inhibitors carbidopa and benserazide.

† Available through Health Canada's Special Access Programme.

Table 2 – Management of treatment-associated motor complications<sup>1,4,6,7,11,18,20,21</sup>

Complication	Management strategy*	Comments
Wearing-OFF	Reduce levodopa dose intervals without changing dose	Considered best approach by some experts; 4–6 daily doses may be sufficient when motor fluctuations are just becoming apparent; in late-stage PD, some patients are prescribed levodopa every 1.5 or 2 hours
	Increase levodopa dose	May be less effective than reducing dose intervals; increases risk of dyskinesias
	Switch to or add CR levodopa	CR levodopa is often used, but clinical trials haven't shown definitive superiority over standard levodopa at reducing OFF time; may be useful for night-time akinesia (nocturnal end-of-dose akinesia) when dosed at bedtime or during the night
	Add COMT inhibitor or MOA-B inhibitor	Evidence insufficient to say which strategy to choose first; on average, these agents reduce OFF time by 1–1.5 hours/day
	Add dopamine agonist	Reduce duration of OFF episodes by ~1.2 hours/day; dyskinesias may occur/worsen (in patients with pre-existing dyskinesias, reducing levodopa doses may minimize this problem)
	Add amantadine or an anticholinergic	May improve disabling recurrent OFF symptoms in some patients who fail to improve with other strategies
Delayed ON/ no ON	Increase levodopa dose	May be needed to reach therapeutic threshold
	Avoid dietary protein with levodopa doses/administer levodopa on empty stomach	May enhance levodopa absorption; gastric emptying can be optimized by stopping or reducing anticholinergic agents
Unpredictable ON–OFF swings	Consider strategies for wearing-OFF and dyskinesias	Evidence is insufficient to determine best management strategies
Peak-dose dyskinesias	Reduce individual levodopa doses	May increase OFF time (increasing the number of daily levodopa doses or adding/increasing dose of dopamine agonist may mitigate problem)
	Discontinue or reduce dose of COMT inhibitor or MOA-B inhibitor	May increase OFF time
	Add amantadine	Usual dose is 200–400 mg/day; benefit may last <8 months
Biphasic dyskinesias	Consider strategies for peak-dose dyskinesias	Evidence is insufficient to determine best management strategies; increasing the size and frequency of levodopa doses may be helpful in instances where peak-dose dyskinesias are absent or are considered less disabling than the biphasic type
OFF-period dyskinesias	Consider strategies for wearing-OFF	May also be beneficial for OFF-period freezing; additional levodopa or dopamine agonist doses at night may be effective for dystonia appearing during the night or early morning; early-morning levodopa administration may also benefit early-morning dystonia

COMT = catechol-O-methyltransferase; CR = controlled-release; MAO-B = monoamine oxidase type B; PD = Parkinson's disease  
 \* The list of options presented is not exhaustive; refer to online guidelines<sup>11</sup> for additional management strategies (see References, below, for URL).

with treatment-related motor complications (see Box 3), making control of motor symptoms difficult to achieve.<sup>7</sup> Potential strategies for dealing with motor complications are outlined in Table 2. When assessing options for treatment modification, it should be kept in mind that many patients prefer being ON with dyskinesia rather than OFF without dyskinesia.<sup>1,11</sup> Most patients will eventually receive a combination of several drugs in an attempt to control motor symptoms and complications; however, the best strategy for combining more than two drugs is uncertain based on available evidence.<sup>7,11</sup>

Surgical approaches should be

considered for patients with severe motor fluctuations or dyskinesias who fail to respond to medical therapies.<sup>1,11</sup>

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