Parkinson’s disease

by Mary Ann E Zagaria, PharmD, MS, CGP

Key points for the pharmacist

Parkinson’s disease (PD) is a progressive neurodegenerative disorder most frequently appearing between the ages of 50 and 79. More than half of all individuals over age 85 may exhibit some signs of parkinsonism (see below). Age is considered a key risk factor in the development of PD, and incidence of the disease increases dramatically with age. Among all age-groups, incidence of PD is 10 to 20 cases per 100,000 but rises to about 200 cases per 100,000 among persons in their 70s and 80s. The umbrella term parkinsonism is often used to encompass PD and related syndromes and generally refers to the motor picture involving bradykinesia (literally ‘slow movement’), rigidity, tremor, and balance and gait problems. Secondary parkinsonism, due to other causes or non-idiopathic parkinsonism, has a different aetiology and pathology than does PD. The posture of a patient with PD becomes stooped with the head drooping forward and resting on the chest, which can be dangerous. When patients lose their balance, their feet and hands cannot move quickly enough to break a fall. While the motor symptoms associated with PD can cause difficulty in performing activities of daily living (ADLs) such as buttoning clothing and tying shoes, the non-motor symptoms may have a greater negative impact on quality of life. Non-motor symptoms include anxiety, depression, confusion, dementia, urinary dysfunction, and excessive daytime sleepiness.

Pathophysiology summary

The common pathological feature in PD and secondary parkinsonism is striatal dopamine deficiency. In patients with PD, cell loss occurs in the substantia nigra with the formation of Lewy bodies (intracellular neuronal inclusion bodies). Lewy bodies are not present in secondary parkinsonism; however, the nigral striatal pathway may be impaired, and nigral cell loss or loss of striatal cellular elements may occur.

Clinical presentation

PD begins subtly and progresses gradually. In its early stages, signs of the disease may be difficult to differentiate from those of normal ageing. Most patients initially present with a slow, coarse tremor of the hand that occurs when the muscles are at rest (resting tremor) and causes the fingers to move across the thumb as if rolling pills (pill rolling). The tremor decreases when the hand is moving purposefully, may be worsened by fatigue or stress, and disappears completely during sleep. While this low-frequency, low-amplitude tremor may progress to the other hand, arms, jaw, and legs, it may become less obvious with progression of PD. Other main symptoms of PD include bradykinesia, rigidity (a tightness or increase in muscle tone while at rest or throughout the entire range of motion of a limb], cogwheel rigidity] that may be described as stiffness by the patient), and postural instability (Table 1).

Additional signs may include a walking pattern that consists of shuffling and short steps without swinging of the arms. Patients often have difficulty stopping or turning while walking and may suddenly and unpredictably freeze in place. In contrast, movements may become unintentionally faster and result in a short-stepped, stumbling run to avoid falling, while speech may become faster, with words running together in a mumble. The posture of a patient with PD becomes stooped with the head drooping forward and resting on the chest, which can be dangerous. When patients lose their balance, their feet and hands cannot move quickly enough to break a fall.

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Additionally, impairment of the autonomic nervous system may lead to constipation, orthostatic hypotension, and excessive sweating.

**PD and dementia**

While there is significant variation among estimates regarding the frequency of dementia in PD, approximately 40% to 50% of patients with PD develop dementia, especially during the late stages of PD and in older individuals. Even patients with PD who do not have dementia show slight cognitive deficits. Dementia-related problems are usually milder than the dysfunction associated with Alzheimer’s disease and are considered part of the pathology of PD. Characteristics seen in patients with both PD and dementia include visuospatial deficits, difficulty planning, impaired attention, slowed speed of processing information, and mildly impaired memory recall; memory impairment is usually attributed to a retrieval deficit, since recognition is generally unaffected. Some language skills (eg vocabulary) are not affected, while others (eg verbal fluency, mechanical aspects of speech) are impaired. Confusion often becomes problematic and is usually worsened by antiparkinson medications.

**Drug- and toxin-induced parkinsonism**

The wide use of antipsychotic agents in elderly patients for the management of behavioural problems has resulted in the recognition of antiparkinsergic-related adverse effects, including extrapyramidal signs and symptoms. These drug-related symptoms may be misdiagnosed as a new medical condition (ie PD) and the patient may be started on antiparkinsergic therapy, thus becoming vulnerable to additional adverse effects (eg delirium, hypotension). Discontinuing or reducing the antipsychotic agent is a more desirable approach. If a neuroleptic is deemed necessary, an agent with a more favourable adverse effect profile at the lowest possible dose is recommended. This also applies to the newer, atypical antipsychotic agents that have adverse effects at higher doses.

**Medications to avoid in the elderly PD patient**

Symptoms of PD will worsen with medications that block dopamine receptors, such as antipsychotic agents (especially the typical antipsychotic agents including haloperidol and chlorpromazine), the antiemetic prochlorperazine, and the gastrointestinal prokinetic agent, metoclopramide. Large doses of vitamin B6 (pyridoxine) should be avoided to prevent the peripheral conversion of levodopa (L-dopa) to dopamine, which interferes with the efficacy of L-dopa therapy. Patients receiving selegiline therapy, associated with an amphetamine metabolite, should not take pethedine, due to interaction and such risks as over-stimulation of the central nervous system (CNS), seizure, hyperpyrexia, hypertension, and hypotension. Ephedrine-like prescription and over-the-counter products should also generally be avoided in these patients. Anticholinergics should always be used cautiously and are best avoided in the elderly.

**Pharmacotherapy**

PD and secondary parkinsonism that is not drug-induced is incurable. Drugs that cause or exacerbate parkinsonism should be discontinued. Patients may not require treatment in the early stages of PD if symptoms do not cause functional impairment. The patient should clearly be involved in deciding when to initiate therapy. The patient’s occupation and ADLs, as well as the risks and benefits of therapy, should be considered. As PD progresses, therapy becomes more complex, requiring dose adjustments, polypharmacy, and the use of rescue treatments. Antiparkinsergic agents (Table 1) tend to cause confusion and toxic psychosis in elderly patients. For this reason, it is generally recommended that the therapeutic regimen be kept as simple as possible, since the risk of adverse effects is lower when one or two agents are given at higher doses as compared to a multiple-drug regimen using lower doses.

Amitriptyline may be used as monotherapy for up to 12 months before the initiation of L-dopa to target mild symptoms including tremor and to reduce L-dopa–induced dyskinesias in later disease. While early dopamine agonist monotherapy has been shown to reduce the subsequent risk of dyskinesias and other motor complications in comparison to L-dopa, it has the potential to cause orthostatic hypotension and neuropsychiatric adverse effects (eg confusion, hallucinations). As a result, these agents should be avoided in patients with confusion, memory or cognitive impairment, and in patients at risk of hypotension.

While anticholinergics improve motor symptoms in some patients with PD (especially younger persons with resting tremor as a predominant symptom), these drugs often produce constipation, sedation, confusion, urinary retention, dry mouth, and blurred vision in the elderly. Furthermore, they are contraindicated in individuals with glaucoma, benign prostatic hypertrophy, and dementia.

Dopamine replacement is accomplished with L-dopa, which should be added to the drug regimen when PD symptoms can no longer be managed optimally with other agents. Since L-dopa is converted to dopamine in the CNS and the periphery, peripheral conversion and systemic effects can be reduced by combining L-dopa with carbidopa (a peripheral decarboxylation inhibitor), which does not cross the blood–brain barrier.
The addition of a catechol-O-methyltransferase (COMT) inhibitor decreases the end-of-dose failure or ‘wearing off’ of L-dopa therapy that causes motor complications. By reducing the peripheral metabolism of L-dopa, a COMT inhibitor allows for the reduction of L-dopa doses. Compared with standard L-dopa therapy, some researchers recommend the initiation of a COMT inhibitor at the onset of L-dopa therapy to reduce the risk of developing motor complications.

In the later stages of PD, dopamine agonists may be added to L-dopa therapy in the appropriate patients, providing greater efficacy and reduced motor complications (as compared to L-dopa monotherapy) due to the ability to lower the L-dopa dose. Patients who have a deteriorating response to L-dopa, experience fluctuations in response to L-dopa, or have a limited clinical response to L-dopa secondary to an inability to tolerate higher doses are appropriate candidates. A decrease in the frequency of ‘off’ periods and a L-dopa–sparring effect can occur with dopamine agonists. Apomorphine, a short-acting, dopamine agonist, is delivered by subcutaneous injection as a rescue dose to manage the sudden and refractory motor fluctuations of L-dopa–induced ‘off’ periods in patients with PD. Its administration is routinely preceded by the anti-emetic, trimethobenzamide hydrochloride (not available in SA) to prevent adverse effects such as nausea and vomiting.

If patients continue to experience unpredictable ‘on’ and ‘off’ periods, a monoamine oxidase type B (MAO-B)

### Table 1

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<thead>
<tr>
<th>Symptoms of Parkinson’s disease medication therapy with antiparkinson agents</th>
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<tr>
<td><strong>Primary symptoms of Parkinson’s disease</strong></td>
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<tr>
<td>Bradykinesia</td>
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<tr>
<td>Muscular rigidity</td>
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<td><strong>Primary symptoms related to the treatment of Parkinson’s disease</strong></td>
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<tr>
<td><strong>Secondary symptoms of Parkinson’s disease and medication therapy</strong></td>
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<tr>
<td>Ankle swelling*</td>
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<tr>
<td>Dementia, memory loss, confusion*</td>
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<tr>
<td>Dizziness and lightheadedness*</td>
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<tr>
<td>Insomnia*+</td>
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<tr>
<td>Micrographia (shaky, tiny handwriting)*</td>
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<tr>
<td>Seborrhoeic dermatitis*</td>
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<td>Speech (eg, monotone, stutter, whisper)*</td>
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<tr>
<td>Sweating*</td>
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<td>Visual problems*+</td>
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*Secondary symptom of Parkinson’s disease. |
+Secondary symptom of medication therapy with antiparkinson agents.

L-dopa: levodopa; GI: gastrointestinal. Source: References 1,4,21
inhibitor or amantadine may be added to the regimen; apomorphine may also be utilised as rescue therapy. Studies on the neuroprotective effects of MAO-B inhibitors have been inconclusive. When confusion and disorientation occurs, discontinuing or lowering the doses of antiparkinsonian drugs is recommended as follows: anticholinergic agents discontinued first, followed by selegiline, dopamine agonists, and L-dopa. The pharmacist plays a critical role in advocating treatment regimens that address administration needs while keeping patient care a priority.

**Primary symptoms related to treatment**

**Dyskinesias:** A complication of L-dopa therapy is dyskinesias-abnormal, choreiform, and involuntary movements usually involving the neck, trunk, and upper extremities. Dyskinesias are usually associated with peak antiparkinsonian benefit, although they can also develop during the rise and fall of L-dopa effects. Dyskinesias can be thought of as too much movement secondary to the extension of the pharmacological effect or too much striatal dopamine receptor stimulation. Dyskinesias are more likely to occur with L-dopa therapy (D, and D, agonism) than with dopamine agonist therapy (primarily D, agonism), suggesting D, receptor involvement in producing dyskinesia. While most patients do not mind mild choreiform movements as a trade-off for good mobility, troublesome dyskinesias should be addressed with strategies aimed at reducing the amount of L-dopa at each dose, as mentioned above, including fractioning L-dopa into smaller but more frequent dosages. End-of-dose failure and the “wearing off” phenomenon: In elderly persons, 30% of hospital admissions may be linked to drug-related problems, and falls leading to hospitalisations are especially likely in patients with PD, particularly those experiencing ‘wearing off,’ a loss of benefit from a dose of L-dopa that typically occurs after a few hours. End-of-dose ‘wearing off’ or deterioration has been related to increasing loss of neuronal storage capability for dopamine. Motor fluctuations may become more severe and dyskinesias occurring during peak dose effect may occur. Modified treatment strategies (mentioned above) should be considered at this point to improve symptoms and allow for reduced doses of L-dopa.

**Surgery**

Information on surgical procedures to relieve symptoms of PD may be obtained by contacting the American Parkinson Disease Association Inc. at www.apdaparkinson.org, via email at apda@apdaparkinson.org.

**Diet**

Since protein ingestion interferes with L-dopa absorption, rearranging the timing of protein-containing meals so that they are consumed in the evening may prevent interference with L-dopa therapy in patients with advanced PD; agents other than L-dopa are not affected by protein ingestion.

**On the horizon**

Rasagiline, a new MAO-B inhibitor currently awaiting FDA approval, has demonstrated monotherapy efficacy in early PD and adjunctive efficacy to L-dopa therapy in later PD. This agent may interact with fluoxetine, pethidine, and tricyclic antidepressants. It is metabolised by cytochromes P-3A4 and P-2D6.

The Committee to Identify Neuroprotective Agents for Parkinson’s has identified a number of compounds as candidates for further study. Of these, minocycline, creatine, CoQ10, and GPI1485 have been selected for testing in the Neuroprotective Clinical Trial. Researchers are examining naturally occurring enzymes that appear to deactivate free radicals, which some scientists think may be linked to the nerve damage in PD and other neurological disorders.

**Conclusion**

To maintain optimal mobility and enhance the quality of life of patients with PD, it is essential that the therapeutic approach be tailored to the individual. As PD progresses, therapy becomes more complex, often requiring dose adjustments, polypharmacy, and the use of rescue treatments. Pharmacists with knowledge of PD and its treatment strategies have the opportunity to serve the patient and become an integral part of the interdisciplinary treatment team.

**References are available on request**