

# Pharmaceutical Treatment of Parkinson's Disease

The best outcomes rely on a handful of medicines and partnership among clinicians, patients, and caregivers.

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Parkinson's disease (PD) is the second most common neurodegenerative disease. It affects an estimated 7 million people worldwide and will affect more than 14 million people



by 2040. PD is diagnosed by the presence of progressive asymmetric bradykinesia and tremor (especially resting tremor) or rigidity, with a sustained response to dopamine-replacement therapy and the development of motor fluctuations and dyskinesia with

long-term therapy. Early motor disability results from degeneration of dopaminergic neurons in the midbrain substantia nigra pars compacta, and dopaminergic medications are the foundation of therapy for motor disability. The critical driver of neurodegeneration in PD is intracellular toxicity of  $\alpha$ -synuclein (AS) oligomers. Over time, the core motor features worsen, and a fluctuating pattern of medication response, progressive gait and balance disorders, and non-motor symptoms emerge, to the detriment of overall function and quality of life. Many changes reflect the spread of pathology throughout the brain over time.<sup>1</sup>

For decades, pharmacotherapy for PD has centered on restoration of dopaminergic activity in the brain. The miracle of levodopa reigns among the most important advances in the history of neurology. Treatment of patients' nonmotor disability is less scientifically based and generally less successful. Management of patients with PD requires a practiced hand, and care provided by a neurologist carries a lower risk of nursing home placement, hip fracture, and death compared to that provided by primary care physicians.<sup>2</sup> This review focuses on pharmacologic management of PD.

## Treating Motor Impairment

Motor symptoms in a patient with PD drive the choice of therapy. Medication initiation is tailored to the individual's

symptoms, lifestyle, and personal responsibilities. Many people do not need medications at the time of diagnosis. Treatment is indicated once their symptoms impair daily activities, work, or recreation. Treatment of motor disability focuses on enhancing dopaminergic activity. Because PD medications have numerous side effects (Table), all are started at low doses and titrated to the lowest effective dose.

## Levodopa Formulations

Levodopa, the precursor of dopamine, remains the most effective medication for motor symptoms of PD. Absorbed in the small intestine, levodopa crosses the blood-brain barrier, is decarboxylated by L-aromatic-acid decarboxylase in neurons of the central nervous system (CNS), and then is released to stimulate striatal dopamine receptors. Levodopa formulations combine an aromatic acid decarboxylase inhibitor (ie, carbidopa or benserazide) to decrease peripheral decarboxylation, reducing side effects of nausea and orthostatic hypotension, and improving CNS bioavailability.<sup>3</sup> Oral carbidopa-levodopa is available in regular and sustained-release formulations (carbidopa-levodopa controlled release), a combination of regular and longer-acting formulations (carbidopa-levodopa extended release), and an orally disintegrating tablet. The dose and administration schedule vary between products depending on time-to-benefit onset and half-life of the individual agents. Standard regular-release formulations have the fastest onset of action (15-30 min), whereas sustained release formulations have a slower onset of action (1-2 hours). The orally disintegrating formulation dissolves rapidly and is swallowed and absorbed in the small intestine. It is helpful when liquid is not available to take pills. Although not supported by pharmacokinetic data, some patients report faster onset of benefit from orally disintegrating formulations compared to regular-release carbidopa-levodopa. Carbidopa-levodopa is active against all motor symptoms of PD and is started at a low dose (~150 mg/day) and titrated to the lowest effective dose. Levodopa is an amino acid and competes with dietary amino

TABLE. PHARMACEUTICAL TREATMENTS FOR MOTOR SYMPTOMS OF PARKINSON'S DISEASE

ACTION	DRUGS	AVAILABLE FORMULATIONS	COMMON SIDE EFFECTS
Dopamine precursor with metabolic inhibitor	Levodopa/carbidopa	Tablets (IR, ER) Dissolving tablets	Nausea, vomiting, orthostatic hypotension, vivid dreams, hallucinations, delusions
MAO inhibitors reduce levodopa and dopamine degradation	Rasagiline	Tablets	Hypertension, orthostatic hypotension, potentiation of levodopa-related side effects
	Selegiline	Tablets, capsules, orally disintegrating tablets	
	Safinamide	Tablets	
COMT inhibitors reduce levodopa and dopamine degradation	Entacapone	Tablets	Potentiation of levodopa-related side effects, diarrhea, orange color of urine
	Tolcapone	Tablets	Potentiation of levodopa-related side effects, hepatotoxicity,
Dopamine receptor agonists	Pramipexole	Tablets, ER tablets	Nausea, vomiting, orthostatic hypotension, hallucinations, psychosis, impulse control disorders, peripheral edema
	Ropinirole	Tablets, ER tablets	
	Rotigotine	Transdermal patches	
	Apomorphine	Subcutaneous injection	
Other/Unknown	Anticholinergics (trihexyphenidyl, benztropine)	Tablets	Dry mouth, dry eyes, confusion, hallucinations, constipation, urinary retention
	Amantadine	Tablets, capsules, ER tablets	Dry mouth, dry eyes, livedo reticularis, confusion, hallucinations, constipation, urinary retention, peripheral edema

Abbreviations: COMT, catechol-*o*-methyltransferase; ER, extended release; IR, immediate release; MAO, monoamine oxidase.

acids for facilitated transport in the gut, thus is best absorbed on an empty stomach. Side effects related to peripheral conversion of levodopa to dopamine, including nausea, vomiting, or orthostatic hypotension, may be remediated by supplemental carbidopa. Patients who fail to respond to doses of levodopa >800 mg per day may have levodopa-resistant symptoms that raise concern for an atypical parkinsonian disorder. Levodopa has a short plasma half life, and the CNS response to levodopa changes over time; this results in development of a fluctuating response to the drug (also known as *motor fluctuations*) and the appearance of involuntary movements (also known as *dyskinesia*), which characterize more advanced PD. Carbidopa–levodopa is also available as a gel for instillation into the small intestine by a jejunostomy tube and pump for patients with advanced PD who have difficult-to-control motor fluctuations.<sup>4</sup>

#### Agents That Alter Metabolism of Levodopa or Dopamine

Dopamine levels in the CNS can be enhanced using monoamine oxidase (MAO) inhibitors or catechol-*o*-methyltransferase (COMT) inhibitors. Both MAO and COMT inhibitors increase CNS dopamine levels by blocking enzymes in the degradative pathway for levodopa or dopamine, thus producing higher CNS dopamine levels. MAO inhibitors may be useful as monotherapy for mild symptoms, and both MAO and COMT inhibitors are often used as adjunctive therapy for motor fluctuations later in the course of PD.

MAO inhibitors include rasagiline and selegiline tablets. The latter is also available as orally disintegrating tablets. A newer agent, safinamide, is an MAO inhibitor with novel glutamate-blocking activity.<sup>5</sup> MAO inhibitors are generally well tolerated. Because they are selective for MAO-B receptors, the risk for tyramine interactions with MAO inhibitors

is low. They may be used with caution in combination with selective serotonin reuptake inhibitors (SSRIs). Selegiline has amphetamine metabolites, which may be helpful in patients with excessive daytime sleepiness.

Entacapone and tolcapone slow the degradation of dopamine by blocking COMT. Entacapone blocks peripheral metabolism of dopamine, and tolcapone blocks COMT both centrally and peripherally. However, tolcapone has been associated with some cases of fatal hepatotoxicity. A combination formulation of carbidopa/levodopa plus entacapone is available. COMT inhibitors enhance levodopa side effects, and entacapone has been associated with secretory diarrhea in some patients.

### Direct-Acting Dopamine Agonists

Dopamine agonists pramipexole, ropinirole, rotigotine, and apomorphine stimulate striatal dopamine receptors. Each differs in affinity for dopamine receptor subtypes, but all are similarly efficacious for treating patients with PD. However, dopamine agonists are less effective and more poorly tolerated than levodopa and require very slow titration. Pramipexole and ropinirole are also available as extended-release products. Rotigotine is available as a transdermal preparation, and apomorphine is available as a subcutaneous injection. Dopamine agonist side effects include nausea, sedation, orthostatic hypotension, and hallucinations. In addition, peripheral edema, excessive daytime sleepiness, and impulse control disorders (eg, gambling, hypersexuality, excessive eating, or excessive spending) can occur. Rapid discontinuation of dopamine agonists may precipitate withdrawal symptoms (ie, anxiety, restlessness, and akathisia).<sup>6</sup>

Dopamine agonists are most helpful as adjunctive agents in patients with difficult motor fluctuations but may also be recommended for use as initial treatment especially in patients under the age of 60 in order to delay development of motor fluctuations and dyskinesia. However, these benefits must be weighed against the poorer efficacy and tolerability of these agents. Given the successful use of deep brain stimulation in PD, there is an increased willingness to prescribe the more efficacious and better tolerated levodopa as initial therapy even in patients with early onset PD. Injectable apomorphine has a rapid onset of action, a short half life, and is used for sudden off periods or early morning akinesia as a bridge between oral levodopa doses.<sup>7</sup> Nausea and orthostatic hypotension are common with injectable apomorphine requiring antiemetic prophylaxis with trimethobenzamide or domperidone.

### Anticholinergics

Anticholinergic medications (eg, trihexyphenidyl, benztropine) can be helpful for tremor that persists despite dopaminergic therapy, and modestly reduce rigidity and dystonia. Side effects may include dry mouth, blurry vision, consti-

tion, urinary retention, sedation, memory impairment, confusion, or hallucinations. More elderly or cognitively impaired patients are particularly sensitive to anticholinergic side effects and should be monitored for cognitive and neuropsychiatric changes.

### Amantadine

The antiviral agent amantadine was serendipitously noted to modestly reduce motor symptoms for patients with PD, likely through antagonism of the NMDA glutamate receptor. Amantadine is most often used to treat patients with PD who have mild motor disability or to reduce the severity of levodopa-induced dyskinesia for patients with more advanced PD. Side effects include sedation, peripheral or corneal edema, livedo reticularis, and hallucinations. Recently, 2 long-acting amantadine products have been approved.

### Treating Motor Fluctuations

Progressive loss of dopaminergic neurons over the course of PD and changes in receptor function produce a syndrome of motor fluctuations, including early morning akinesia, wearing off of benefit between doses, unpredictable off periods, dose failure, and dyskinesia. Medication adjustments include increasing dose frequency, using longer-acting levodopa preparations, or adding a dopamine agonist, MAO inhibitor, or COMT inhibitor. Patients can be taught to recognize motor fluctuations and make minor adjustments in their levodopa schedule.

Ultimately, there are as many schedules for the treatment of motor disability in PD as there are patients with PD. Finding the right schedule for any patient requires a partnership among providers, patients, and caregivers.

### Treating Levodopa-Resistant Motor Signs

Speech and swallowing dysfunction in patients with PD tends to persist despite optimal medications and thus requires close collaboration with speech and language pathology colleagues. Speech therapists can be helpful in addressing hypophonia and can teach strategies to optimize communication. Although speech dysfunction is often present at diagnosis, dysphagia usually occurs later in the disease course. Bedside swallow assessments or videofluoroscopy may guide dietary and behavioral modifications.<sup>8</sup>

Gait impairment and postural instability with falls are among the most disabling physical symptoms of PD. In treated PD, gait includes dopamine-responsive and dopamine-resistant components. Gait freezing, the temporary inability to produce effective forward stepping, is among the more troublesome symptoms. The threshold of benefit for freezing may be higher than that for other signs (pseudoresistance), so it may be helpful to increase dopaminergic

therapy as the first strategy.<sup>9</sup> However, many patients notice increased dopaminergic therapy is ineffective and sometimes harmful. These patients may benefit from physical therapy efforts to explore visual cueing strategies, improve safety measures, and assess the need for walking aids.<sup>9</sup> Occupational therapists can assist in adapting a patient's environment and routine. Rehabilitative therapies help to address for postural instability, which is often poorly responsive to medications.

Tremor can also remain troublesome despite adequate dopaminergic therapy for bradykinesia and rigidity.<sup>10</sup> Although in some cases, higher levodopa doses may be helpful in treating a patient with levodopa-resistant tremor, this symptom may also be an indication for deep brain stimulation treatment.

## Treating Nonmotor Impairments

### Treatment of Autonomic Symptoms

Autonomic dysfunction results in burdensome symptoms including neurogenic orthostatic hypotension (nOH), gastrointestinal problems (eg, constipation, dysphagia, and sialorrhea), urinary problems, and sexual dysfunction. A general treatment paradigm is shown in the Figure.

Fatigue and cognitive impairments are worsened by nOH and can lead to syncope.<sup>11</sup> Volume depletion and anemia should first be corrected then discontinuation of any antihypertensives vasodilators prescribed for comorbidities (eg, sildenafil,  $\beta$ -blockers) should be considered. Levodopa and dopamine agonists lower blood pressure; smaller doses with shorter dosing intervals to mitigate this effect should be considered. Reducing alcohol, high-glycemic index carbohydrates, and large meals prevents excess diuresis and postprandial hypotension. If not contraindicated, salt and caffeine intake should be liberalized. Patients with nOH should move slowly when transitioning from sitting to standing and avoid precipitants such as long hot showers and excessive straining during bowel movements. Elevating the head of the bed can reduce diuresis triggered by supine hypertension. High-waist compression stockings and abdominal binders augment venous return, but are cumbersome, thus unpopular solutions. When pharmacologic treatment is required, fludrocortisone expands intravascular volume by increasing sodium reabsorption. A vasoconstrictor such as midodrine or droxidopa is the next step. Midodrine induces a relatively short-lived vasoconstrictor effect and can be dosed with levodopa, which helps offset a levodopa-induced drop in blood pressure. An alternate vasoconstrictor is the norepinephrine precursor droxidopa. Supervised dose titration is aimed at symptomatic improvement during the patient's most active periods of the day.<sup>11</sup> Pyridostigmine, a cholinesterase inhibitor, can also be used.

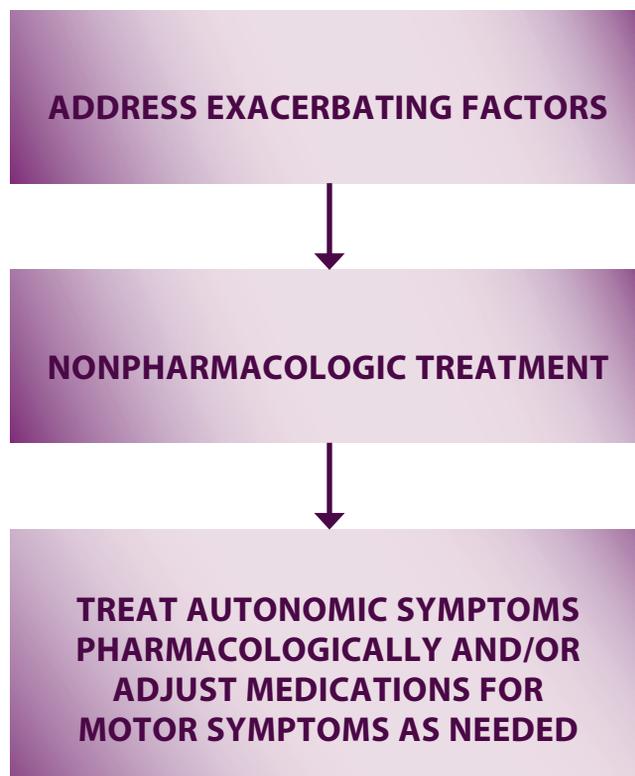


Figure. Treatment of autonomic symptoms. A stepwise approach to the treatment of autonomic symptoms can be useful.

Gastrointestinal dysfunction occurs at all levels and in all phases of PD.<sup>12</sup> Sialorrhea results from impaired swallowing and can be worse during off periods, when the patient's symptoms are less responsive to levodopa. Reducing salivary production with botulinum toxin injections into the salivary glands or with oral, transdermal, or sublingual anticholinergics may be helpful. Glycopyrrolate is efficacious. Treatments under investigation include scopolamine patches, atropine drops, and sublingual ipratropium bromide spray.<sup>13</sup>

Autonomic dysfunction reduces colonic motility in patients with PD, causing constipation. The first step in treatment is to minimize constipating medications (eg, opioids, antihistamines, anticholinergics) and recommend sufficient hydration, physical activity, and a diet rich in high-fiber foods. Probiotics can be useful for some patients, and anticonstipation fruit paste may be a more palatable alternative to over-the-counter or prescription laxatives.<sup>14</sup> When these measures are inadequate, a stool softener or osmotic laxative can be added. Oral bulking agents should be used with caution, as these can make stool more difficult to pass. Stimulant laxatives that increase colonic motility are generally not recommended for daily use because of side effects (eg, bloating, cramping, diarrhea), but can be effective in some patients. Although there is insufficient evidence to rec-

commend newer medications such as plecanatide, linaclotide, or lubiprostone for patients with PD, these may be used under supervision from a gastroenterologist. Appropriate and timely treatment of constipation helps prevent serious complications (eg, impaction or bowel perforation), improves absorption of medications, and reduces symptoms from lower urinary tract dysfunction.

Frequent urination, urinary urgency, nocturia, and incontinence are common manifestations of neurogenic detrusor overactivity in PD.<sup>15</sup> Behavioral modifications such as timed voiding and restricting fluids late in the day may be helpful. Long-acting dopaminergic medication at bedtime or intranasal desmopressin may reduce nocturia. Antimuscarinic medications that relax the detrusor muscle (eg, solifenacin, trospium, darifenacin) or the  $\beta$ -3 agonist mirabegron may be helpful. However, antimuscarinic agents with higher CNS penetration such as oxybutynin and fesoterodine should be avoided because these have cognitive side effects.

Sexual dysfunction (erectile or ejaculatory dysfunction, decreased libido, difficulty achieving orgasm, vaginal dryness) affects many patients with PD. Comorbid conditions (eg, cardiovascular disease, prostatic hypertrophy, depression, or anxiety) or treatment for comorbid conditions (eg,  $\beta$ -blockers, 5 $\alpha$ -reductase inhibitors, or SSRIs) may also play a role in sexual dysfunction in patients with PD. Sildenafil can be effective for treating erectile dysfunction and lubricants may be helpful for patients with vaginal dryness. Hypersexuality is one of the impulse control disorders that are a side effect of dopaminergic treatment that should be treated.

### Treating Neuropsychiatric Symptoms

Fatigue may be an independent symptom of PD and/or a symptom of depression and sleep disturbances that are often present in patients with PD. The first step in treating a patient's fatigue is to optimize motor function and sleep. Although the evidence for efficacy of amantadine to treat fatigue in patients with PD is not convincing, it is commonly prescribed in clinical practice. Clinical trials have not supported the use of stimulant medications for treatment of fatigue in patients with PD, and stimulants are considered investigational.<sup>16</sup>

Depression in patients with PD is usually characterized by sadness and anhedonia, but other changes (eg, sleep, appetite, energy, affect) can be difficult to differentiate from the primary symptoms of PD.<sup>17</sup> In the absence of a clear consensus regarding specific antidepressants in patients with PD, treatment choices are based upon an individualized risk vs benefit assessment. Nortriptyline and desipramine are considered likely efficacious for treatment of depression in patients with PD but may have unacceptable cognitive or autonomic side effects. Selective norepinephrine reuptake inhibitors (SNRIs) and SSRIs are also

efficacious and are commonly used in clinical practice.<sup>18</sup>

Anxiety is common in patients with PD, frequently in association with depression. Anxiety may fluctuate in concert with motor fluctuations, a pattern that may respond to optimizing motor function. Cognitive behavioral therapy, SSRIs, and SNRIs can be anxiolytics. Routine use of benzodiazepines is not recommended because of the cognitive side effects, tolerance, and dependence that frequently occur.<sup>19</sup>

Up to 40% of patients with PD develop apathy and loss of motivation and interest in activities that may accompany depression but is distinct from it in that sadness is not always present.<sup>20</sup> Aside from treating comorbid mood disorders and ensuring adequate dopaminergic therapy, treatment options for apathy symptoms are limited.

Most patients with PD will experience psychotic symptoms over the course of the disease, though severity varies widely. Hallucinations are more common than delusions. Risk factors for psychosis include higher dopaminergic doses, older age at disease onset, longer disease duration, cognitive impairment, and presence of rapid-eye-movement sleep behavior disorder. Correcting vision and hearing impairments decreases the risk of having psychotic symptoms. When psychosis occurs acutely, reversible causes such as infection, dehydration, metabolic disturbances, intoxication, or recent medication changes should be sought. Treatment includes eliminating any sedating or psychoactive drugs and streamlining medications for PD. A sound initial approach is to first withdraw anticholinergic medications, then amantadine, followed by MAO and COMT inhibitors and dopamine agonists. Carbidopa/levodopa should not be withdrawn, although dose reductions may be necessary. Cholinesterase inhibitors may reduce mild visual hallucinations in the setting of cognitive impairment. If psychotic symptoms persist and cause distress, treatment with atypical antipsychotics may be indicated. Quetiapine is often used, although its use is not supported by the evidence. Clozapine and pimavanserin have been shown to reduce psychotic symptoms in patients with PD. Clozapine is associated with agranulocytosis and requires frequent monitoring. Pimavanserin, with a unique mechanism of inverse agonism at a specific serotonin receptor (5-HT<sub>2A</sub>), does not worsen parkinsonian motor signs, and was approved by the Food and Drug Administration for treatment of psychosis specifically related to Lewy body disorders in 2016.<sup>21</sup> Other typical and atypical antipsychotics may be associated with motor decline, and should not be used for patients with PD.

Cognitive dysfunction increases in prevalence and severity with disease progression in patients with PD. The patient's cognitive status should be screened annually, and the emergence of cognitive symptoms should prompt a medication

review, with withdrawal of potentially offending medications as outlined for psychosis. Depression, anxiety, and poor sleep should be addressed, and exercise and social engagement should be encouraged. Pharmacotherapy for cognitive dysfunction in patients with PD is limited to symptomatic treatments that have only modest efficacy. There is some cognitive benefit from treatment with the cholinesterase inhibitors donepezil and rivastigmine, although they have gastrointestinal side effects and may worsen tremor.<sup>22</sup> A trial period of a cholinesterase inhibitor, allowing titration to the target dose and observation by caregivers, is a reasonable approach. The NMDA receptor antagonist memantine has failed to demonstrate consistent benefit and can worsen visual hallucinations.<sup>23</sup>

## Neuroprotective Treatments

Neuroprotection or disease modification in PD remains an elusive goal. The critical driver of neuronal pathology appears to be AS-oligomer–derived neurotoxicity. Downstream of AS, therapeutic targets include oxidative stress, mitochondrial dysfunction, excitotoxicity, inflammation, and apoptosis.<sup>24</sup> Potential therapies aimed at these targets have failed in clinical trials. Several factors are responsible for these disappointing results. First, given the many intracellular consequences of AS toxicity, single agents might be expected to fail. Second, heterogeneity inherent in the disease may dilute any disease-modifying effect. Third, the loss of striatal dopamine appears to be complete within a few years of diagnosis for most patients with PD, suggesting it might be important to initiate disease-modifying interventions in the prodromal stage of the illness. Newer approaches to experimental therapeutics will likely target synucleinopathy, earlier diagnosis and treatment, and different outcome measures.

## Summary

Successful management of the many clinical aspects of PD over a protracted and progressive clinical course can lead to rewarding improvements in patients' quality of life. However, there is room for improvement, particularly in late-stage illness, suggesting a need for new therapeutic targets and approaches. Particularly compelling is the need for neuroprotective interventions. However, at present, the best outcomes rely on a handful of medication classes and a therapeutic partnership among the provider, patient, and care partners. ■

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