

## Parkinson's Disease: Improving Symptom Control with Pharmacotherapy

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**Goal.** The goal of this lesson is to provide information on Parkinson's Disease and its pharmacotherapy.

**Objectives.** At the completion of this activity, the participant will be able to:

1. describe the epidemiology of Parkinson's Disease, including estimated incidence and prevalence;
2. recognize signs and symptoms, and key clinical features of Parkinson's Disease;
3. select the indication, pharmacologic action, clinical application, pharmacokinetic parameters, and mode of administration for each drug;
4. demonstrate an understanding of adverse effects and toxicity, warnings, precautions, contraindications, and significant drug-drug interactions reported for each agent; and
5. list important information to convey to patients and/or their caregivers.

### Background

Although evidence of Parkinson's Disease (PD) can be found earlier, James Parkinson first described the disorder as a neurological syndrome in his 1817 *Essay on the Shaking Palsy*. Traditional Indian texts dating to approximately 1000 B.C. and ancient Chinese sources

of the same era also provide pathological descriptions that suggest PD. In succinct English, Parkinson clearly captured the clinical picture: "Involuntary tremulous motion, with lessened muscular power, in parts not in action and even when supported; with a propensity to bend the trunk forward, and to pass from a walking to a running pace: the senses and intellect being uninjured."

The affliction was further characterized by Charcot in 1872, who first referred to it as Parkinson Disease, therefore acknowledging James Parkinson's earlier work. Nearly 100 years would then pass before effective treatment became available. Discovery in the late 1950s that dopamine was a pivotal neurotransmitter in the brain was a landmark accomplishment in understanding PD. Clinical trials of the dopamine precursor, levodopa, followed in the 1960s with discovery that it was an effective agent for treatment of PD. Despite these advances, however, the ultimate cause of PD remains as elusive now as it was when first described by Parkinson.

### Epidemiology

Reported PD prevalence and incidence rates vary greatly because of different criteria used for defining it; differences in case-finding methodologies and incidence studies; variation in follow-up periods to identify PD conversion; and in

excluding comorbidities. A review of the literature lists a prevalence rate of approximately 1 percent in persons 60-years-old. Prevalence rates increase with advancing age with the greatest reported occurrence approximately 2.5 to 4 percent at age 80 years and over. Thus, PD affects more than one million Americans, which exceeds the combined number of people diagnosed with multiple sclerosis, muscular dystrophy, and ALS (amyotrophic lateral sclerosis [Lou Gehrig's disease]). An estimated seven to 10 million individuals globally are living with the disease. Men are one and a half times more likely to have PD than women. Prevalence is expected to markedly increase in the coming decades due to aging of the population. Estimates are that by the middle of this century, 80 million people in the United States will be older than 65 years and approximately 20 percent of them will exceed 85 years. Thus, healthcare professionals can expect to see more patients with diseases more commonly associated with old age. This will certainly be the case with PD. The Parkinson's Disease Foundation estimates that the current combined direct and indirect costs of PD in the United States are \$25 billion annually, with medication costs for an individual averaging \$2,500 a year.

**Table 1**  
**Cardinal motor features of Parkinson's Disease\***

*Bradykinesia/akinesia* (early onset)

- Slowed movement, fatiguing with decreased amplitude of movement, arrests in ongoing movement
- Decreased spontaneous movements such as eye blinking, swallowing, and arm swing

*Tremor* (early onset)

- Rhythmic sinusoidal movement of a body part due to regular contractions of reciprocally innervated muscles (either synchronous or alternating)
- Occurs at rest

*Muscle rigidity* (early onset)

- Increase in resistance to passive movement
- “Cogwheel” rigidity: a combination of leadpipe rigidity and tremor which presents as a jerky resistance to passive movement as muscles tense and relax
- Patients may complain of stiffness but not a major source of disability

*Postural change* (late onset)

- Flexed posture
- Postural instability – retropulsion, propulsion, falls (*en bloc* [as a whole])

*Gait disorder* (late onset)

- Shuffling, lack of arm swing
- Festination: gait marked by involuntary hurrying in walking
- Freezing: feet “sticking to the floor like glue,” occurs with turning, gait initiation, enclosures like doorways

\*Adapted from Smith Y, Wichmann T, Factor SA, and DeLong MR. *Neuropsychopharmacology Reviews*. 2012;37:213-246.

## Pathophysiology

PD is a progressive neurodegenerative disorder defined pathologically as degeneration of dopaminergic neurons in the substantia nigra, a region of the midbrain. The hallmark sign of PD is the presence of ubiquitous Lewy bodies in these neurons that serve as histological correlates of cell death. Lewy bodies are fibrillar aggregates of  $\alpha$ -synuclein, a protein that develops inside nerve cells in PD and other central neurological pathologies. They appear as spherical masses that displace other cell components, and are usually present in the regions showing the most neuron loss. Pathologic changes may be detected up to 20 years before onset of motor symptoms.

PD has a major impact on patients' quality of life. Overall mortality remains higher in PD patients than in the general population. Moreover, while dopamine

neuron loss remains the most prominent pathologic feature of the disease, this loss spreads over the course of the disease to almost the entire CNS. This extensive broad-range pathology is likely responsible for the nonmotor features of PD, such as depression, anxiety, sleep disorders, sexual dysfunction, cognitive dysfunction, olfactory dysfunction, anhedonia (total loss of feeling of pleasure in acts that normally give pleasure), and orthostatic hypotension. As therapy for the motor features has improved, these nonmotor aspects have become important sources of disability for patients. Death frequently results from complications of immobility, including aspiration pneumonia or pulmonary embolism.

Several disorders other than idiopathic PD also may produce parkinson-like symptoms (parkinsonism) including some relatively

rare neurodegenerative disorders, stroke, and intoxication with dopamine-receptor antagonists. A complete discussion of the clinical response to these drugs, differential diagnostic features of PD, and the nonmotor complications of PD exceed the scope of this lesson.

## Treatment of Parkinson's Disease

Availability of effective pharmacotherapy has greatly altered the prognosis of PD. In most patients, functional mobility can be maintained over many years with proper drug treatment, and life expectancy of adequately treated patients can be increased substantially.

PD treatments have largely focused on correcting the brain's dopaminergic deficit, thereby alleviating the cardinal motor symptoms: bradykinesia (slowed movement), rigidity, resting tremor, and gait disturbances (Table 1). When it was first discovered that PD was caused by depleted dopamine levels in the brain, the obvious task was to enhance the dopaminergic response. This approach was ineffective with orally administered dopamine, as it does not cross the blood-brain barrier. The next step was to administer a drug that would cross the blood-brain barrier to increase dopamine centrally. Such a chemical, levodopa, already existed. Since its introduction into therapy in the 1960s, a variety of other therapies have also been developed (Table 2). The agents in Table 2 are effective in symptom control, particularly in the early stages of PD. A neuroprotective therapy that slows, stops, or reverses disease progression is the most important need in PD therapeutics. To date, no drug has been demonstrated to have neuroprotective or restorative effects in PD.

**Levodopa.** Levodopa (L-DOPA; Larodopa, and others) is the gold-standard treatment for PD. Levodopa is effective in reducing motor symptoms of PD for virtually all patients, particularly in the early stages of the disease. This recommendation is supported

by the Practice Guidelines of the American Academy of Neurology. If a patient takes levodopa at doses greater than 1,000 mg/day and there is no alleviation of symptoms, an alternative diagnosis should be considered.

Levodopa is largely inert, with both therapeutic and adverse effects resulting from its decarboxylation to dopamine within the CNS. Taken orally, the drug is absorbed rapidly from the small intestine via the transport system for aromatic amino acids. Plasma concentrations following oral administration usually peak in 0.5 to two hours and plasma half-life is short, one to three hours. Both rate and extent of absorption depend on the rate of gastric emptying, pH of gastric juice, and length of time the drug is exposed to degradative enzymes of the gastric and intestinal mucosa. Competition from dietary protein for absorption sites in the small intestine also plays a pivotal role in determining the extent of drug absorption.

Levodopa's passage across the blood-brain barrier into the CNS also is mediated by a membrane transporter for aromatic amino acids within neurons; thus, competition between dietary protein and levodopa may also occur at this level. Once dopamine has been released into the central synaptic spaces, it can be transported back into dopaminergic terminals, or metabolized by monoamine oxidase (MAO) and catechol-O-methyltransferase (COMT) enzymes.

Taken alone, levodopa is largely decarboxylated by intestinal enzymes so that relatively little unchanged drug, perhaps as little as 1 percent, reaches the cerebral circulation. Moreover, dopamine released into the circulation by peripheral conversion of levodopa can produce undesirable effects including nausea and vomiting. Thus, levodopa is almost always used in combination with carbidopa (as Sinemet), a peripherally acting inhibitor of aromatic amino acid decarboxylase. Inhibition of peripheral decarboxylase activity

<b>Drug/Drug Class</b>	<b>Examples</b>	<b>Advantages</b>
Precursor to dopamine (levodopa) with carbidopa (decarboxylase inhibitor)	Sinemet (immediate- & sustained-release); carbidopa enhances CNS absorption of levodopa	Most effective, improves disability, prolongs ability to perform daily activities
Dopamine-receptor agonists	Pramipexole (Mirapex), Ropinirole (Requip), Bromocriptine (Parlodel, etc.), Rotigotine (Neupro)	Can be used as monotherapy in early disease or added to levodopa/carbidopa to treat motor complications; rotigotine is available as transdermal patches.
Injectable dopamine-receptor agonist	Apomorphine (Apokyn)	Reduces <i>off</i> time in late disease. Useful in patients unable to take oral medications.
Monoamine oxidase-B (MAO-B) inhibitors	Selegiline (Eldepryl) Rasagiline (Azilect)	Can be used as monotherapy in early disease, or to treat motor complications in early disease
Catechol-O-Methyltransferase (COMT)	Entacapone (Comtan) Tolcapone (Tasmar)	Used to treat motor complications, adjunct to levodopa/carbidopa; no titration, decreased <i>off</i> time, mild improvement in daily activities and quality-of-life scores.
Anticholinergics	Benzotropine (Cogentin) Trihexyphenidyl (Artane)	Useful to treat tremor in patients younger than 60 years without cognitive impairment
N-methyl-D-aspartate inhibitor	Amantadine (Symmetrel)	Treat dyskinesia in late disease

\*Adapted from Gazewood JD, Richards DR, and Clebak K. *Am Fam Physician.* 2013;87:267-273.

substantially increases the amount of administered levodopa that remains unmetabolized and hence able to cross the blood-brain barrier. It also reduces the incidence of adverse gastrointestinal effects.

Levodopa's action on signs and symptoms of PD can be dramatic. The extent of improvement in tremor, rigidity, and bradykinesia may be nearly complete in early disease. In fact, the duration of benefit of levodopa may exceed its plasma half-life, meaning that the brain's dopamine neurons may be

able to store and release dopamine.

A major drawback to long-term levodopa use is that over time, the majority of patients eventually experience a narrowing of the therapeutic window, resulting in fluctuating motor response with each successive dose of the drug. A familiar complication is development of the phenomenon in which each dose of levodopa improves symptoms for a period of time, but symptoms such as rigidity and akinesia (loss or impairment of voluntary activity [as of a muscle])

return rapidly at the end of the dosing interval, a period known as *off* time. This is of particular interest, as this is arguably the biggest contributor to functional impairment in patients with advancing PD. Increasing levodopa dosage and/or shortening the dosing interval may improve this situation, but this often is limited by onset of dyskinesia (spontaneous, involuntary muscle movements) or dystonia (involuntary muscle movement that can bend the body into abnormal, unstable, and sometimes painful positions). These responses can be as uncomfortable as the rigidity and akinesia of PD. In advanced stages of PD, patients may fluctuate rapidly between *on/off* periods, and the medication will suddenly and unpredictably start or stop controlling symptoms. This is referred to as the *on/off phenomenon*. The ability to reduce *off* time without an associated increase in motor symptoms is an important goal of therapy development.

**Levodopa/Carbidopa Intestinal Gel Therapy.** An underlying force behind the *on/off phenomenon* is theorized to be fluctuating plasma dopamine concentrations (high peaks, low valleys) of circulating levodopa associated with oral administration. This theory is strengthened by the finding that COMT inhibitors that increase the half-life of levodopa will decrease motor fluctuations, and that longer-acting agents can treat or prevent these complications. Thus, development of new delivery technology to provide more sustained levels of the therapeutic dopaminergic agents may be a useful approach to minimize unwanted adverse effects.

Intestinal infusion of levodopa/carbidopa intestinal gel (LCIG) is an effective means of reducing motor symptoms. LCIG produces the same pharmacotherapeutic outcome as oral levodopa administration. This therapeutic approach requires surgical placement of a percutaneous enteroduodenal/jejunal tube. Its use has been reserved for patients with advanced disease,

and particularly those who are not candidates for surgical therapy. Early attempts to use levodopa in this manner were cumbersome and complicated by solubility issues.

Following approval in Europe in 2004, a formulation and delivery device that relies on duodenal or proximal jejunal infusions of levodopa in a viscous carboxymethylcellulose aqueous gel (trademarked Duodopa™) was entered into U.S. clinical trials. Early studies with Duodopa revealed high rates of device-related problems with the intestinal tube such as clogging, kinking, and becoming dislodged from its correct location. The gel medium prevents levodopa/carbidopa from settling out in the solution and avoids clogging of administration tubes. This form of treatment is reportedly safe and appears to provide significant improvement in motor fluctuations over various oral dopamine-related drug combinations. However, adverse effects such as movement of the cannula within or from the intestine, and irritation and erosion of the skin around the port warrants continued investigation before this approach can be safely used as routine PD treatment. If approved, Duodopa will offer a tremendous advantage for many patients with *on/off* fluctuations, and will, in most cases, permit discontinuation of many oral drugs.

Thus far, clinical trials show that motor symptoms and non-motor ramifications seem to be ameliorated and quality-of-life issues improved with LCIG. However, results of these trials need to be questioned carefully since many of the available data originate from open-label and/or observational studies. LCIG may be especially suited for older patients with late sequelae of levodopa therapy such as motor complications and for patients with a high risk of hallucinations.

**Dopamine-Receptor Agonists.** Agents that are direct stimulants of the brain's dopamine receptors offer an alternate choice and potential benefit over levodopa.

The duration of action (eight to 24 hours) of dopamine-receptor agonists exceeds that of levodopa and may be effective in patients who experience the *on/off phenomenon*. Finally, it has been theorized that dopamine-receptor agonists may modify the natural course of PD by reducing endogenous release of dopamine and the need for exogenous levodopa.

Two dopamine-receptor agonists are available for oral administration: ropinirole (Requip) and pramipexole (Mirapex). These have largely replaced older agents (bromocriptine, pergolide) that need to be titrated more slowly. Pergolide was withdrawn from the U.S. market in 2007 because of its propensity to cause cardiac valvular disease and pleuropulmonary/retroperitoneal fibrosis. The Rotigotine Transdermal System (Neupro) is a newer dopamine agonist approved for treatment of PD, as well as restless legs syndrome.

Both ropinirole and pramipexole are well absorbed orally and have similar actions to modify the clinical symptoms of PD, although the drugs have a less desirable short-term risk profile compared to levodopa. Both drugs may produce confusion or hallucinations similar to that observed with levodopa. Both may cause nausea and orthostatic hypotension. The drugs, as well as levodopa itself, are also associated with fatigue and somnolence, which can be quite severe. They have also been linked with onset of compulsive behaviors, such as heightened sexual urges, gambling, and shopping.

Apomorphine (Apokyn®) is a potent subcutaneously-administered dopaminergic agent that cannot be used orally due to extensive hepatic first-pass metabolism. Double-blind clinical trials have repeatedly confirmed its effectiveness in improving PD motor symptoms. The drug is rapidly absorbed after subcutaneous injection, and has a half-life of 30 to 60 minutes. Apomorphine can be considered for use in patients with PD when they are not able to take oral medications,

such as when hospitalized or when in a postoperative state. Clinical improvement occurs within 10 to 20 minutes of administration. The drug can be administered as an intermittent subcutaneous bolus or continuous subcutaneous infusion. Intermittent bolus doses offer effective rescue therapy for increasing the duration of *on* phases, while continuous infusion via portable pump delivery can lessen daily *off* time and reduce the required doses of oral PD drugs. Development of alternative delivery methods such as sublingual, intranasal, rectal, transdermal, or intravenous administration may eventually make apomorphine a more attractive choice in treatment of PD.

The primary autonomic adverse effects of apomorphine are the same as those for other dopamine-receptor agonists (i.e., nausea, hypotension, and drowsiness/sleep disturbance). Psychiatric problems appear to be less prevalent with intermittent apomorphine injections than with other agonists, perhaps because of the drug's short half-life. Apomorphine administration can induce injection site reactions and skin nodules in almost all patients, leading not only to cosmetic considerations, but also to interrupted drug absorption. Thus, alternating injection sites is warranted. The most common adverse reactions to apomorphine are severe nausea and vomiting. It is recommended to administer an anti-emetic three days prior to initiation of apomorphine therapy, and to continue it for two months before reassessing need. Apomorphine is contraindicated with 5HT<sub>3</sub> antagonists. In clinical trials, this was addressed effectively by administering trimethobenzamide (Tigan, and others) several days before the first application, although 31 percent of patients still experienced nausea and 11 percent experienced vomiting.

Eventually, use of apomorphine may produce psychiatric effects, including hallucinations or acute psychotic syndrome, particularly in patients with preexisting psychiat-

ric conditions. Due to the common comorbidity of motor fluctuations and psychiatric symptoms in later stages of PD, apomorphine use is hence restricted. For most patients suffering from motor complications in the earlier stages of PD, the drug remains a good choice to provide satisfactory immediate and long-term results.

The rotigotine patch has shown efficacy across all stages of PD. The precise mechanism of action of rotigotine in PD is unknown, although it is believed to stimulate central dopamine receptors. Since rotigotine is administered transdermally, food does not affect its pharmacokinetics and the product may be administered without regard to the timing of meals.

Rotigotine can cause or worsen psychotic-like behaviors including hallucinations, aggressive behavior, disorganized thinking, and can cause hypotension. Patients may experience onset of compulsive behaviors with rotigotine, as has been shown with ropinirole and pramipexole.

#### **Selective MAO Inhibitors.**

Two isoenzymes of MAO, termed MAO-A and MAO-B, metabolize monoamines. Both forms are present peripherally and inactivate monoamines, including dopamine of intestinal origin. MAO-B is the predominant form in the CNS and is responsible for the majority of dopamine metabolism in the brain.

Two selective MAO-B inhibitors, selegiline (Eldepryl<sup>®</sup>, and others) and rasagiline (Azilect<sup>®</sup>), are used for treatment of PD. These agents selectively inactivate MAO-B and, thereby, exert modest benefit in suppressing PD symptoms via inhibition of breakdown of dopamine in the brain. In contrast to nonspecific MAO inhibitors such as phenelzine and tranylcypromine, the MAO-B inhibitors have little action on the peripheral metabolism of dopamine and can be taken concurrently with levodopa. Moreover, the selective inhibitors do not cause the potentially lethal potentiation of catecholamine action that can occur when patients taking

nonspecific MAO inhibitors ingest indirectly-acting sympathomimetic amines such as tyramine (present in certain cheeses and beer.)

Selegiline is normally well tolerated in young patients who have early or mild PD. In more advanced disease or in patients with cognitive impairment, selegiline may accentuate adverse motor and cognitive actions of levodopa. Amphetamine and methamphetamine are metabolites of selegiline and can accentuate anxiety, insomnia, and other adverse symptoms. Two novel delivery systems are available for selegiline, an orally disintegrating tablet (Zelapar<sup>®</sup>), and a transdermal patch (Emsam<sup>®</sup>). Emsam is indicated for treatment of major depressive disorder. Both are intended to reduce hepatic first-pass metabolism to limit formation of the undesirable metabolites. Rasagiline is not metabolized to these metabolites.

The selective MAO-B inhibitors are generally well tolerated, but drug interactions can be bothersome. Selegiline can cause agitation, hyperthermia, stupor, and rigidity when given with meperidine. Neither selegiline nor rasagiline should be given concurrently with meperidine. Serious, sometimes fatal, reactions have been noted with MAO-B inhibitors coadministered with tricyclic antidepressants, serotonin-reuptake inhibitors, or tramadol. Coadministration of selegiline or rasagiline with serotonergic agents should be undertaken only with extreme caution, especially with high doses of serotonin-reuptake inhibitors. Symptoms of serotonin syndrome have included behavioral and cognitive/mental status changes (e.g., confusion, hallucinations), autonomic effects (e.g., syncope, hyperthermia, hypertension), and somatic effects (e.g., musculature rigidity, myoclonus, hyperreflexia).

**Catechol-O-methyltransferase Inhibitors.** COMT inhibitors also prevent the metabolic breakdown of levodopa. Their primary action, like MAO-B inhibitors, is to extend the duration of action of

levodopa. COMT inhibitors have a propensity to augment dopaminergic effects, such that levodopa doses might need to be adjusted downward.

Two COMT inhibitors are available in the United States, tolcapone (Tasmar<sup>®</sup>) and entacapone (Comtan<sup>®</sup>). These agents have no direct effect on PD symptoms, but instead are used to prolong the effect of levodopa by blocking its metabolism. The drugs differ from one another primarily in their pharmacokinetic profiles and adverse effects. Entacapone has a short duration of action and is usually administered simultaneously with each dose of levodopa/carbidopa. Tolcapone's longer duration of action permits administration two to three times a day. It acts by both central and peripheral inhibition of COMT.

Adverse effects of both agents resemble those of levodopa/carbidopa and include nausea, confusion, orthostatic hypotension, vivid dreams, and hallucinations. Tolcapone's label contains a Boxed Warning of hepatotoxicity. Fatal cases of fulminant hepatic failure in patients taking tolcapone have been observed. Its use, therefore, should be limited to patients who are unresponsive to other therapies and always with appropriate monitoring for hepatic injury. Entacapone is not associated with hepatotoxicity and its use does not require special monitoring.

**Non-Dopaminergic Therapies.** Several miscellaneous drugs are occasionally prescribed. They may be of benefit in selected cases.

**Anticholinergic Agents.** Antagonists of muscarinic acetylcholine receptors are the oldest therapeutic agents utilized in PD, dating back to the late-1800s. Initially, naturally occurring belladonna alkaloids were used, including atropine and scopolamine. In the 1950s, synthetic formulations of muscarinic receptor blockers such as trihexyphenidyl (Artane, and others) and benzotropine mesylate (Cogentin) were developed. It was postulated that the dopaminergic

deficit in PD led to an increase in striatal cholinergic activity that contributed to tremor and other symptoms. Today, the basis for their therapeutic action in PD remains unknown. There are surprisingly few trials of anticholinergic drugs in PD, and most were carried out more than 30 years ago. In general, benefit was found to be much less robust than with levodopa. The effect is believed to be most notable for rigidity and tremor.

In practice, the use of these drugs is limited, used only in treatment of early PD or as an adjunct to dopaminergic therapy. Because anticholinergic drugs are poorly tolerated by the elderly, they are most often used in young patients with tremor-predominant disease and dystonia.

Anticholinergic drugs are associated with a range of adverse effects, including memory loss, confusion, hallucinations, constipation, urinary symptoms, dry mouth, dry eyes, and blurred vision through cycloplegia. All anticholinergic drugs must be used cautiously, if at all, in patients with narrow-angle glaucoma. These drugs can cause or increase dyskinesia in PD patients as well.

**Amantadine.** Originally approved as antiviral therapy for prophylaxis and treatment of influenza A, amantadine (Symmetrel) also has mild antiparkinsonian activity. Its action in PD is not clear, but may involve both anticholinergic activity and inhibition of N-methyl-D-aspartate. Interference with other neurotransmitters is also feasible. It may be of benefit for therapy in young people and as adjunct therapy in patients who are taking levodopa and experience dose-related fluctuations and dyskinesia. Amantadine is well tolerated with potential adverse effects including dry mouth, constipation, bladder problems, ankle swelling, and skin rash.

## Initiating Therapy

Determining when to initiate drug therapy for PD should be individually tailored to a patient's symp-

toms, circumstances, and comorbidities. Treatment is indicated when symptoms interfere with the patient's quality of life. There is no solid evidence to support undue delay in starting treatment because of concerns about levodopa toxicity or development of treatment resistance. Some patients may be reluctant to start treatment with pharmacotherapy early on. Most clinicians agree that delaying initiation of treatment is unwise, and may place patients with PD at risk for falls. The goal of therapy is to control symptoms and maintain an *on* state. Motor features of early PD typically respond well to dopamine replacement therapies. The choice of drug therapy includes carbidopa/levodopa, a dopamine-receptor agonist, or an MAO-B inhibitor.

Levodopa, in conjunction with carbidopa, has the greatest efficacy for motor symptoms and tends to be well tolerated, particularly when started in low doses. The simplest dosing regimen is to start with a specific dose at a set time, and, thereafter, monitor efficacy in terms of the dose required for symptom relief and the duration of that response. With disease progression, it is important to establish the dose that relieves increasing symptoms. This usually requires increasing the frequency of dosing from three to four or more times a day, with addition of a long-acting preparation at bedtime. It is important to note that while PD medications help with motor symptoms, there may be limited improvement in postural stability and dynamic function with these drugs. This implies that the risk of falls increases with progression of PD, and thus, patients will need to use assistive devices (e.g., canes, walkers), and participate in physical therapy and exercise to reduce risk from falls.

Until recently, numerous clinical trials suggested there were no significant differences in outcomes between patients started on levodopa with carbidopa and those given dopamine-receptor agonists. It is

common to initiate therapy with a dopamine-receptor agonist in persons aged <50 years, and levodopa/carbidopa in those >70 years.

A June 2014 report summarized the outcome of a large, pragmatic trial that assessed treatment outcomes during a follow-up period of three to seven years. Treatment was initiated in 1620 patients with early PD: levodopa (528 patients), a dopamine-receptor agonist (632 patients), or an MAO-B inhibitor (460 patients). The study revealed there were small but persistent benefits from initial therapy with levodopa, and initial MAO-I therapy was at least as effective as a dopamine-receptor agonist.

### Inadequate Response

It is important to exclude other diseases if the patient's symptoms are not controlled. As PD progresses slowly, any sudden deterioration suggests presence of a coexistent nonmotor medical condition, such as a urinary tract infection, or non-adherence with therapy.

Sustained failure to achieve adequate symptom control with a particular levodopa or dopamine-receptor agonist regimen should signal that the dose of that drug needs to be increased or consideration given to combination therapy. A fluctuating or erratic treatment response in early PD may reflect variable absorption of oral therapy. Administering levodopa on an empty stomach can improve drug absorption. Consideration of drugs that provide more continuous dopaminergic stimulation, such as once-daily pramipexole or the rotigotine patch, may be of benefit.

Nocturnal symptoms may be improved with addition of a long-acting dopamine-receptor agonist, particularly if the patient has restless legs, or dosing with a controlled-release levodopa/carbidopa product. Nonmotor symptoms may also require appropriate therapy.

Some patients with tremor refractory to levodopa may respond to dopamine-receptor agonists. Anticholinergic drugs can be administered cautiously in younger

patients, and are occasionally beneficial in reducing saliva production. They can, however, cause significant cognitive adverse effects such as hallucinations, particularly in older adults.

### Adherence to Treatment Protocol

Strict adherence to treatment protocol is essential to maximize therapeutic benefit and maintain PD symptom control, and poor adherence has been associated with a low quality of life. Quality of life in patients with PD depends on the severity of their disease, along with availability of safe and effective pharmacotherapy. There must also be significant patient satisfaction with the quality of medical and pharmaceutical care to ensure a high degree of quality of life. A survey of 500 patients conducted in the United States and Europe revealed that patients with early and advanced PD were generally less satisfied with their pharmacotherapy than patients with other chronic conditions such as rheumatoid arthritis or asthma.

Dissatisfaction with healthcare professionals who are supervising treatment may contribute to the considerable rate of drug non-adherence that has been observed in persons with PD. These patients, especially those older than 65 years, often take 10 or more doses of medications each day for control of motor symptoms, along with a multitude of treatments for various nonmotor comorbidities. In all likelihood, they have complex treatment regimens that will be compounded over the course of the disease, and medication administration may be complicated even more by interfering problems associated with motor and nonmotor symptoms.

There is a positive association between patient satisfaction, in terms of open communication with all healthcare professionals, and adherence intent. This strongly indicates that adherence may be improved when healthcare professionals take a proactive stance to

ensure a patient-centered approach to care.

### Overview and Summary

It is estimated that the combined annual direct and indirect costs of PD in the United States are a staggering \$25 billion. With a rapidly growing number of Americans reaching 60 years of age and beyond, the prevalence of PD and its effect on the U.S. economy can be expected to increase dramatically. PD has a significant negative effect on the quality of life of patients and their caregivers, with much of the impact originating from nonmotor symptoms of the disease. Fortunately, treatments for motor symptoms are effective in limiting the disability and improving quality of life associated with the disease.

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*The authors, the Ohio Pharmacists Foundation and the Ohio Pharmacists Association disclaim any liability to you or your patients resulting from reliance solely upon the information contained herein. Bibliography for additional reading and inquiry is available upon request.*

This lesson is a knowledge-based CE activity and is targeted to pharmacists in all practice settings.

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# continuing education quiz

## Parkinson's Disease: Improving Symptom Control with Pharmacotherapy

1. According to a literature review, the prevalence of Parkinson's Disease (PD) in persons 60-years-old is approximately:

- a. 0.5 percent.
- b. 1 percent.
- c. 2 percent.
- d. 5 percent.

2. All of the following statements are true about PD EXCEPT:

- a. it is a progressive neurodegenerative disorder.
- b. the hallmark sign is the presence of Lewy bodies in the brain.
- c. pathologic changes may be detected up to 20 years before onset of motor symptoms.
- d. overall mortality in PD patients is lower than that in the general population.

3. PD treatments have largely focused on correcting the brain's deficit of:

- a. acetylcholine.
- b. dopamine.
- c. norepinephrine.
- d. serotonin.

4. The gold-standard therapy for treating PD is:

- a. apomorphine.
- b. bromocriptine.
- c. levodopa.
- d. selegiline.

5. Competition from dietary protein for absorption sites in the small intestine plays a pivotal role in determining the extent of absorption of:

- a. levodopa.
- b. ropinirole.
- c. selegiline.
- d. tolcapone.

6. All of the following statements about levodopa are true EXCEPT:

- a. its duration of benefit may exceed its plasma half-life.
- b. over time, patients experience a narrowing of the therapeutic window.
- c. plasma concentrations following oral administration usually peak in three to five hours.
- d. it is almost always administered with carbidopa.

Completely fill in the lettered box corresponding to your answer.

- 1. [a] [b] [c] [d]
- 2. [a] [b] [c] [d]
- 3. [a] [b] [c] [d]
- 4. [a] [b] [c] [d]
- 5. [a] [b] [c] [d]
- 6. [a] [b] [c] [d]
- 7. [a] [b] [c] [d]
- 8. [a] [b] [c] [d]
- 9. [a] [b] [c] [d]
- 10. [a] [b] [c] [d]
- 11. [a] [b] [c] [d]
- 12. [a] [b] [c] [d]
- 13. [a] [b] [c] [d]
- 14. [a] [b] [c] [d]
- 15. [a] [b] [c] [d]

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- 1. Rate this lesson: (Excellent) 5 4 3 2 1 (Poor)
- 2. Did it meet each of its objectives?  yes  no  
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- 6. Comments/future topics welcome.

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7. Involuntary muscle movement that can bend the body into abnormal, unstable, and painful positions is:

- a. dyscholia.
- b. dyschezia.
- c. dyskinesia.
- d. dystonia.

8. All of the following statements about LCIG are true EXCEPT:

- a. it is generally ineffective for reducing motor symptoms.
- b. it produces the same pharmacotherapeutic outcome as oral levodopa administration.
- c. use is reserved for patients with advanced disease.
- d. the gel medium prevents the drug contents from settling out in the solution.

9. The following drug has a less desirable short-term risk profile compared to levodopa.

- a. Apomorphine
- b. Entacapone
- c. Amantadine
- d. Ropinirole

10. Rotigotine is available as a(an):

- a. oral tablet.
- b. intestinal gel.
- c. subcutaneous injection.
- d. transdermal patch.

11. Apomorphine cannot be administered orally due to:

- a. lack of absorption following oral administration.
- b. extensive hepatic first-pass metabolism.
- c. nearly complete destruction by gastric enzymes.
- d. interaction with dietary protein.

12. Which of the following inhibits MAO-B?

- a. Entacapone
- b. Rasagiline
- c. Ropinirole
- d. Trihexyphenidyl

13. Selegiline coadministration with all of the following should be undertaken with caution EXCEPT:

- a. tricyclic antidepressants.
- b. serotonin-reuptake inhibitors.
- c. tramadol.
- d. carbidopa.

14. The following drug label contains a Boxed Warning for hepatotoxicity.

- a. Tolcapone
- b. Entacapone
- c. Rasagiline
- d. Amantadine

15. Amantadine:

- a. has major antiparkinsonian activity.
- b. may be of most benefit to older adults.
- c. is well tolerated.
- d. may not be of benefit as adjunct therapy with levodopa.

To receive CE credit, your quiz must be received no later than October 15, 2017. A passing grade of 80% must be attained. CE credit for successfully completed quizzes will be uploaded to the CPE Monitor. CE statements of credit can be printed from the CPE Monitor website. Send inquiries to opa@ohiopharmacists.org.