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AN ONGOING CE PROGRAM
of the University of Connecticut
School of Pharmacy

EDUCATIONAL OBJECTIVES

After participating in this activity pharmacists will be able to:

- Discuss Parkinson's disease (PD), its common and difficult-to treat symptoms, and current guidelines
- Outline new PD medication advancements that improve adherence to PD therapy
- Explain treatment approaches for depression, orthostatic hypotension, psychoses, and sleep disturbances in patients who have PD
- Describe medication management during the perioperative deep brain stimulation (DBS) placement period

After participating in this activity pharmacy technicians will be able to:

- Recall common symptoms of Parkinson's disease and the typical medications used to treat them
- Identify typical and atypical problems associated with Parkinson's disease
- Recognize when to refer patients to the pharmacist for recommendations



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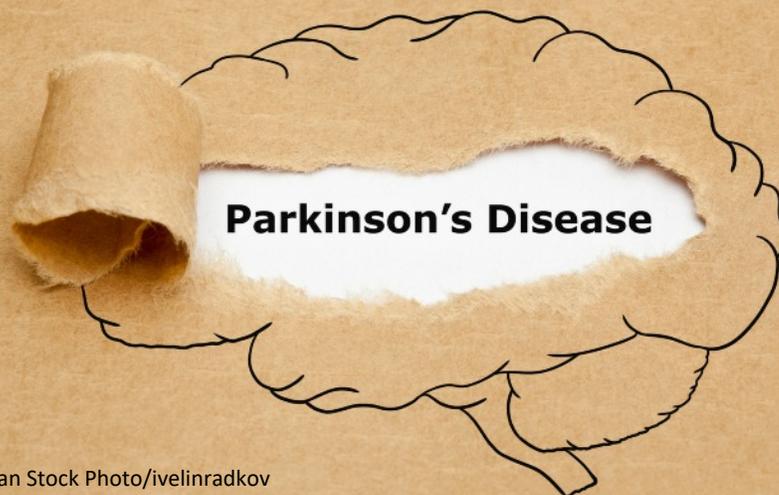
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Proficient in Parkinson's: Understanding Symptoms, Patient Impact, and Medication Advancements

ABSTRACT: Parkinson's disease (PD) is a chronic, progressive illness and the second most common neurodegenerative disease in the United States (U.S.). As the clinical picture of PD worsens, additional medications, increased doses, and increased dosing frequencies are needed to control symptoms. Often considered a movement-related disorder, PD's non-motor symptoms that do not affect movement directly have a substantial impact on quality of life. Pharmacologic treatment is effective; levodopa is the gold standard. Pharmacy teams should be up-to-date on newer treatments to treat motor and non-motor symptoms and cognizant of PD patients' ever-changing clinical picture. Clinicians often suggest that patients whose symptoms persist despite careful, appropriate medication management consider surgical options – either ablative surgery or deep brain stimulation (DBS). Most patients will remain on PD medications post-DBS, but many will substantially lower their daily doses. Rarely, a patient may be able to stop medications completely, but pharmacy teams should help set realistic patient expectations. Non-motor symptoms also have a vast impact on quality-of-life for PD patients and pharmacy teams should be sure they are adequately addressed.

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INTRODUCTION

Parkinson's disease (PD) is the second most common neurodegenerative disease in the United States (U.S.). Clinicians diagnose about 60,000 cases of PD annually, and estimates predict that nearly one million people will be living with PD in the U.S. by 2020. It is a chronic illness that generally develops later in life, after age 60, but an estimated 4% of people with PD are diagnosed before age 50.^{1,2} PD's cause remains unknown, and no cure exists. One disproportionately affected population offers some clues about one cause of PD. The Chamorro people of Guam are disproportionately afflicted with neurodegenerative diseases like PD; this phenomenon is caused by the food chain. Flying foxes, found predominantly

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PAUSE AND PONDER: How many of your patients have Parkinson’s disease? What symptoms are most noticeable?

in Guam, feed on neurotoxic cycad seeds, and then the Chamorro people consume the flying foxes. Neurotoxin accumulation in this traditional Chamorro food leads to accumulation of neurotoxins in the human body.³ While the disease itself is not fatal, complications caused by PD can be serious and are the 14th leading cause of death in the U.S.

Motor PD symptoms develop slowly over years and disease progression varies between patients.² PD’s four cardinal features can be easily remembered using the acronym TRAP⁴:

- Tremor at rest
- Rigidity
- Akinesia (or bradykinesia)
- Postural instability

Rest tremor is the most common and easily recognized PD symptom. Tremors are typically unilateral (occurring on only one side of the body), and while they typically occur in the distal part of an extremity, the lips, chin, jaw, and legs can also be affected. Rest tremor should be differentiated from essential tremor, which can affect the neck/head or voice. Rigidity is characterized by increased resistance during passive movement of the limbs, resulting in start-and-stop movements through the range of motion of a joint, like the elbow. This is also referred to as the “cogwheel” phenomenon. Akinesia is the loss or impairment of the ability to make voluntarily movements, whereas bradykinesia refers to slow movement.⁴

Bradykinesia is PD’s most salient clinical feature. Slowness in completing activities of daily living and slow movement and reaction times are often the initial manifestations. Fine motor control is often affected, making tasks like buttoning or using utensils more difficult. Other manifestations of bradykinesia also include⁴

- loss of spontaneous movements or gestures
- drooling due to impaired swallowing
- difficulty speaking or articulating
- loss of facial expression
- decreased blinking, and
- reduced arm swing while walking.

PD patients generally experience postural instability in the later stages of the disease. It occurs due to the loss of postural reflexes and increases fall risk in PD patients.

Additionally, freezing/motor blocks are among PD’s classic features. Freezing, a form of akinesia, most commonly affects the legs during walking, but arms and eyelids can also be involved. While all patients do not experience freezing episodes, this can be the most disabling symptom, making tasks



like crossing a busy street more difficult and even dangerous.⁴ Patients often experience freezing when turning around in close quarters, so caregivers should encourage PD patients to take wider turns when possible. Other ways caregivers can help with freezing episodes are⁵:

1. Encourage the patient to stop, straighten posture, and shift weight to one foot before trying to step with the other
2. Count or clap a rhythmic beat for the patient to respond and walk to
3. Offer a visual cue, such as “step over my foot”

Often, PD is only considered as a movement-related disorder, when in reality it is more debilitating. Non-motor symptoms (NMS)—those symptoms that do not affect movement directly—have a substantial impact on PD patients’ quality of life. Examples of NMS include^{6,7}:

- Mood changes (depression)
- Sleep disorders and daytime sleepiness
- Difficulty swallowing or chewing
- Speech changes
- Gastrointestinal (GI) disturbance (urinary incontinence, constipation)
- Increased secretions (sweat, saliva)
- Difficulty focusing
- Difficulty with visual-spatial relations
- Visual hallucinations

The VCU Parkinson’s & Movement Disorders Center conducted a survey in 2012 among patients with PD to determine which areas of treatment were adequately addressed.⁶ Participants felt that care for NMS was needed. This survey’s findings with regard to NMS identify a serious gap in care; most patients were receiving no service for care of NMS. Participants reported sleep, cognitive function, and mood fluctuations as the three most troublesome NMS, however, they went untreated. Common misconceptions of PD are shown in **Table 1 (next page)**.

Table 1. Common Misconceptions about Parkinson’s Disease⁷

Myth	Fact
PD always causes a tremor, and tremor is always a sign of PD	PD is highly individualized, appearing with different symptom variations and severity in each patient; tremors can be caused by other conditions, including stroke, multiple sclerosis, or traumatic brain injury.
PD causes uncontrolled, spontaneous movements	Uncontrolled movements in people with PD are dyskinesias; they are not caused by the disease but rather by an imbalance of PD medications
If a person has PD, it explains any symptom they are experiencing	Some symptoms, like shortness of breath, chest pain, sudden speech difficulty, or vertigo are not caused by PD and require immediate medical attention
PD is a genetic disorder	The cause of PD is not yet known; sometimes PD runs in families, but ~90% of cases are sporadic with no family history of the disease
Levodopa stops working after five years	While it doesn’t treat all symptoms of PD, levodopa can effectively manage symptoms for decades
PD is predictable and follows a similar pattern in all patients	Every PD patient is unique, and even an expert neurologist cannot predict exactly how the disease will progress

Notable celebrities have suffered from PD. Doctors diagnosed Michael J. Fox—well-known star of the classic “Back to the Future” movie series—with PD at just 29 years old in 1991. After seven years, he made his diagnosis known to the public and shortly after founded the Michael J. Fox Foundation for Parkinson’s Research. The foundation is actively seeking a cure for PD.⁸ Muhammad Ali— world famous champion boxer—was also diagnosed with early-onset PD at 42 years old.⁹ Medical historians say that Adolf Hitler had PD, too. This is evidenced by his clever positioning in photos to conceal his tremor, and the gradual illegibility of his signature over the course of 22 years.¹⁰

The disease itself has also made its way onto TV and film screens. In *Love and Other Drugs*, a handsome drug salesman meets a woman with early onset PD. Sparks fly, and the film highlights PD’s strain on their relationship. The Michael J. Fox Show was a comedy inspired by his life, where the actor himself played a news-anchor diagnosed with PD who temporarily puts his career on hold for the disease.¹¹

ETIOLOGY OF PD

PD’s cause remains largely unknown, but appears multifactorial, with both genetic and environmental factors contributing. PD is generally considered idiopathic (of unknown origin), and while only a minority of cases report a family history and research has suggested some possible gene mutations that could contribute.¹² Research has found some correlations—positive and negative—with PD and environmental factors. For example, studies show that people with red hair are more likely to develop PD. Dopamine, which is severely deficient in PD, is made from levodopa. The pigment that colors hair red is also made from levodopa, so it’s hypothesized that red hair contributes to dopamine deficiency.¹³

PD is a neurodegenerative disorder that affects dopaminergic (dopamine-producing) neurons, mainly in the substantia nigra area of the brain. The substantia nigra is a pigmented nucleus in the ventral midbrain consisting of dopaminergic neurons associated with movement and reward feedback systems.^{2,12} By the time symptoms are noticeable, approximately 30% of dopamine neurons have already been lost. This increases to about 60% as PD progresses. The result of neuronal degeneration is diminished dopamine levels in the striatum, which is responsible for PD’s cardinal motor symptoms. PD also affects non-dopaminergic neurotransmitter systems, such as the cholinergic, adenosinergic, glutamatergic, GABAergic, noradrenergic, serotonergic, and histaminergic systems. Degeneration of these systems is thought to produce some of the NMS of PD that are unresponsive to dopamine-replacement therapies.¹²

PD patients typically experience great relief from motor symptoms in the initial stages of treatment with dopaminergic medication therapy. However, PD is a progressive disease, and as PD’s clinical picture worsens, additional medications, increased doses, and increased dosing frequencies are needed to control symptoms. Motor fluctuations—also known as “on-off” fluctuations—are a common phenomenon PD patients experience. When symptoms are adequately controlled by medication, this is referred to as “on time.” As medication begins to lose its effect (“wearing off”), patients may experience increased motor symptoms, known as “off time.” As PD progresses, levodopa (used first-line in PD treatment) stays effective for shorter periods of time, requiring more frequent doses and unpredictable “off” episodes. “Off” episodes are not exclusive to motor symptoms; some patients say that NMS can be aggravated during “off time” as well. Symptoms can include pain, anxiety, fatigue, mood changes, difficulty focusing, and more.⁵

Table 2. Unified Parkinson Disease Rating Scale for Assessing PD Severity¹⁴

Subscale	Parameters
Subscale 1: Mentation, behavior, and mood	1. Intellectual impairment (memory loss) 2. Thought disorder (hallucinations) 3. Depression 4. Motivation and initiative (disinterest in hobbies, etc.)
Subscale 2: Activities of daily living	1. Speech 2. Salivation 3. Swallowing 4. Handwriting 5. Cutting food/handling utensils 6. Dressing 7. Hygiene 8. Turning in bed/adjusting bedclothes 9. Falling (unrelated to freezing) 10. Freezing when walking 11. Walking 12. Tremor in right arm 13. Tremor in left arm 14. Sensory complaints (numbness, tingling)
Subscale 2: Activities of daily living	1. Tremor at rest 2. Action tremor 3. Rigidity 4. Bradykinesia (each body part) 5. Speech 6. Facial expression 7. Arising from chair 8. Posture 9. Gait 10. Postural stability 11. Bradykinesia (whole body)
Subscale 4: Complications of therapy	1. Dyskinesias – duration, disability, pain, early morning dystonia (cramping) 2. Clinical fluctuations – predictability of “off times”, presence of sudden “off times”, percentage of day spent “off” 3. Other complications – GI complaints, sleep disturbances, orthostasis*
*orthostasis = a sense of lightheadedness or actual fainting due to a drop in blood pressure associated with standing	

Fall risk is an important consideration in PD patients, and a major quality of life determinant. Orthostatic hypotension, vision changes, gait instability, freezing, dyskinesias, and rigidity are just some of the PD symptoms that can increase fall risk. About 70% of falls occur due to turning, incorrect weight shifting, and inaccurate stepping. Appropriate exercise (discussed below) can reduce fall risk in PD patients.¹⁵

Polypharmacy—the regular use of five or more medications—is also associated with increased fall risk. Some studies also show an association between sleep medications and falls in PD, and others link falls with some antidepressants and neuroleptics.¹⁶ Pharmacists and technicians should counsel patients to establish familiar surroundings that are free of tripping hazards, like area rugs and power cords. Encourage caregivers not to move furniture or add new pieces without letting the person who has PD know. Also, encourage patients to use railings whenever possible (on stairs, in shower, etc.), avoid multi-tasking while walking, and take their time when standing up.¹⁷

PAUSE AND PONDER: Among your patients who have PD, how many are being treated for depression? Does the number seem high, low, or just about right?

TREATMENT APPROACHES

Pharmacologic Treatment

Early-stage PD includes patients who have had the disease for less than five years or who have not developed motor complications from levodopa use. Some mild symptoms can be addressed with monoamine oxidase-B (MAO-B) inhibitors, amantadine, or anticholinergics, but most patients need levodopa or a dopamine agonist. Generally, dopamine agonists are used in patients with mild disease or with onset of PD at a younger age, whereas levodopa is initiated in older patients with severe motor symptoms.

Carbidopa/Levodopa

Levodopa has been used to treat PD for half a century and remains the most effective medication available and first-line treatment for symptomatic PD patients.^{18,19} Levodopa is an immediate precursor to dopamine, meaning it is converted to dopamine in the body. Dopamine itself is too electrically charged to move across the blood-brain barrier into the brain to supplement dopamine neurons in PD patients. Levodopa, however, is able to cross this barrier by facilitated amino acid transport. Levodopa controls bradykinesia and rigidity most effectively; however, speech, postural reflex, and gait disturbance may also show improvement.¹⁹ Pharmacists should reassure patients who are unenthusiastic about starting levodopa that it is a “natural” substance, found normally in the human body for meta-

bolic processes. It is even present in some foods.¹⁸

Levodopa is always given in conjunction with carbidopa. Carbidopa blocks the enzyme dopa decarboxylase to prevent the peripheral (further from the center of the body) breakdown of levodopa before it reaches its final destination, the brain. The effects are two-fold; carbidopa increases cerebral levodopa bioavailability and reduces peripheral adverse effects of dopamine (nausea, hypotension, etc.). A carbidopa dose of at least 70 mg to 100 mg daily is required to prevent nausea and vomiting in patients taking levodopa, so patients typically start immediate-release carbidopa/levodopa at a dose of 25/100 mg three times daily.¹⁹

Disease progression and changes in the GI tract can cause a decline in treatment response to carbidopa/levodopa. An extended-release (ER) carbidopa/levodopa capsule is also available for patients with significant “off times” and wearing off. Patients on carbidopa/levodopa ER may experience up to an hour and a half less “off time” daily.²⁰ Patients with advanced PD who are still responding to levodopa therapy but experiencing motor fluctuations—“off times” for three or more hours daily—may also benefit from the enteral formulation of carbidopa/levodopa. This formulation is delivered continuously through a feeding tube, which administers the gel formulation directly to the small intestine.²¹ Patients experiencing “off times” may also benefit from levodopa inhalation for immediate relief of symptoms. Administered via inhaler up to five times a day, it improves “off” symptoms between doses of carbidopa/levodopa in as soon as 10 minutes and provides up to 60 minutes of relief.²²

Other novel levodopa delivery methods are in development to improve bioavailability. An “accordion pill” containing both immediate-release and extended-release drug formulations is also currently in development. The pill slowly releases medication in the stomach over eight to 12 hours for more steady absorption and stable symptomatic control.^{22,23} Two companies are also currently developing pumps for continuous subcutaneous delivery of carbidopa/levodopa. These, in contrast to the enteral pump, would not require surgery for tube placement.²² Although levodopa remains the most effective medication for PD, pharmacists should be aware of novel delivery methods that could help patients experiencing “wearing off.”

Dopamine Agonists

Dopamine agonists (DAs)—including pramipexole, ropinirole, and rotigotine—are used commonly in PD treatment. Rather than convert into dopamine, they mimic it to stimulate dopamine receptors directly in the brain, improving motor symptoms and reducing “off time.” While studies show that levodopa is more effective at reducing UPDRS scores than DAs, researchers also noted a lower incidence of motor complications with DAs due to their longer duration of action. Injectable apomorphine, another

PAUSE AND PONDER: What types of PD medications do you carry? How many of your patients have symptoms that would suggest a different medication, or a different dosage form?

DA, is approved to treat sudden, unexpected, and resistant “off periods”; it should only be used in the event of emergency.^{19,24} DAs’ side effects are similar to those of carbidopa/levodopa, and also include hallucinations, sleepiness, and compulsive behaviors (hypersexuality, gambling, over-eating, etc.).²⁴ Pharmacists should advise patients on DAs to contact their prescriber if they develop new compulsive behaviors.

Pramipexole and ropinirole are available orally in both immediate-release and extended-release formulations. Ropinirole is metabolized mainly by CYP1A2, so pharmacists should be conscious of drug interactions with CYP1A2 inducers and inhibitors. This includes cigarette smoking, which is a CYP1A2 inducer and could significantly prevent the body from maintaining steady levels of ropinirole. Additionally, ciprofloxacin is a CYP1A2 inhibitor and increases ropinirole levels.²⁵ Pramipexole, however, is excreted mainly in the urine, about 90%, almost completely as unchanged drug, making drug interactions less of a concern. Pharmacists and technicians should note that cimetidine, available over-the-counter (OTC), does in fact interact with pramipexole. It does this by inhibiting renal tubular secretion, thereby increasing pramipexole concentrations and half-life.²⁷ Pramipexole and ropinirole can both be taken without regard to food, however taking them with food may lower the chances of nausea.^{25,26}

Rotigotine is available as a transdermal patch that is replaced daily and delivers rotigotine continuously for 24 hours. This delivery mechanism may be more convenient for patients with adherence barriers, including impaired ability to swallow, as is common in PD. Pharmacist counseling points for rotigotine patches include²⁷:

- Apply at approximately the same time every day, at a convenient time for the patient
- Apply the adhesive side of the patch to clean, dry, intact, healthy skin on the front of the abdomen, thigh, hip, flank, shoulder, or upper arm
- Press the patch firmly onto the skin for 30 seconds, especially around the edges
- Change application site daily, and do **not** apply to the same spot more than once every 14 days
- If applying to a hairy area, shave at least three days prior to patch application

Patients can apply multiple patches at once to reach the desired daily dose of rotigotine. Of note, rotigotine does not have any drug interactions within the CYP450 enzyme system.²⁷

Monoamine Oxidase-B Inhibitors

MAO-B inhibitors – including selegiline, rasagiline, and safinamide – cause a mild decrease in motor fluctuations in PD patients. Monoamine oxidase-B is an enzyme that works to break down dopamine, so by inhibiting this enzyme, MAO-B inhibitors block the breakdown of dopamine in the brain.¹⁹ Selegiline is available in a standard oral formulation and orally-disintegrating tablets (ODTs). This ODT formulation is preferred for patients with PD who have swallowing difficulties. The body converts selegiline to an amphetamine-like byproduct. This can cause adverse effects like jitters or confusion, but it can also help with excessive daytime fatigue.²⁸ Rasagiline, available only as a standard oral tablet, does not have the same byproduct, and therefore does not cause the same side effects selegiline does. Headaches are also common with MAO-B inhibitors, as is indigestion.²⁸

Safinamide is a newer MAO-B approved as an add-on therapy for PD patients on carbidopa/levodopa experiencing excessive “off times.” It is shown to reduce “off time” by up to 55 minutes per day without causing dyskinesia.²² Interactions with MAO-B inhibitors include anti-depressants, decongestants, narcotic painkillers, and foods with high tyramine content (draft beer, aged cheeses, etc.).²⁸ Safinamide also interacts with the cough medicine dextromethorphan, so pharmacy teams should advise patients to check their cold medicine for this ingredient before using.^{22,28}

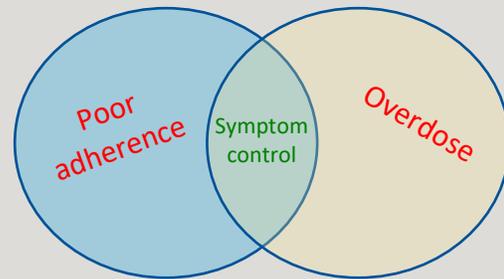
Catechol-o-methyl transferase (COMT) Inhibitors

COMT inhibitors—entacapone and tolcapone—have no effect on PD symptoms, and are therefore never used alone. They are used to prolong the effects of levodopa by blocking its metabolism. Entacapone is available both alone and in a combination pill with carbidopa/levodopa. COMT inhibitors and MAO-B inhibitors should not be used together, as they have very similar mechanisms of action. COMT inhibitors’ common side effects include GI upset (nausea, constipation, diarrhea), abdominal pain, confusion, hallucinations, and discoloration of the urine (reddish brown or rust-colored). Pharmacists should counsel on the possibility of urine discoloration to avoid the patient becoming upset by an orange/brown tinge in the urine and discontinuing therapy unnecessarily. Pharmacy technicians should be sure to affix auxiliary labels (and pharmacists should ensure they are on the bottle at final check); communication – both written and verbal – is key to prevent unnecessary medication discontinuation or misuse. Tolcapone can also cause liver failure, so pharmacists should make note of other medications that affect the liver, causing added stress to the organ.²⁸

Other Pharmacological Options

Anticholinergic medications—trihexyphenidyl and benztropine—treat tremor and dystonia in PD patients associated with “wearing off” or “peak dose” effects. They do not act directly on the dopaminergic system; instead, they decrease the activity of acetylcholine, which regulates movement. Patients older than 70 years should not use anticholinergics, as they are more susceptible to drug-induced confusion and hallucinations. The concomitant use of anti-histamines, anti-psychotic medications, and alcohol should also be avoided. Potential side effects include dry mouth, blurred

Walking the Amantadine Tight-Rope^{29,30}



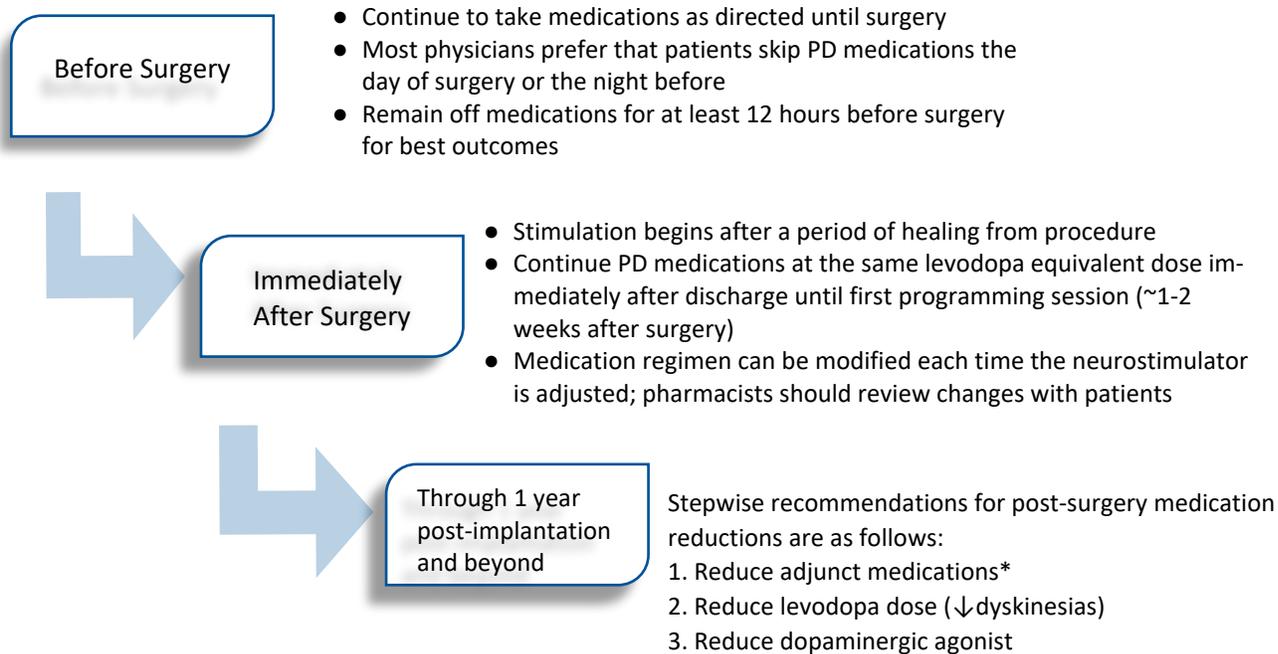
For PD patients, the balance between too little and too much amantadine is delicate. *Poor adherence* leads to poor symptom control, and abrupt discontinuation of amantadine can lead to severe exacerbation of PD symptoms, confusion, acute delirium, and even neuroleptic malignant syndrome (NMS). NMS causes life-threatening fever, muscular rigidity, and altered mental status; pharmacists should counsel on the signs and symptoms of NMS and counsel patients/caregivers suspecting NMS to seek emergency medical attention.

Overdose or amantadine poisoning can cause arrhythmias, agitation, visual hallucinations, nightmares, disorientation, delirium, slurred speech, ataxia, myoclonus, tremor, and sometimes seizures. Urinary retention is also possible, and can lead to obstructive acute renal failure. In the event of a single overdose, stomach pumping can sometimes prevent seizures and eventual coma; when overdosing happens over time, it can be much harder to treat. Pharmacy teams should always review dosing and directions with patients to ensure they take the medication properly.

vision, constipation, and urinary retention.²⁸

Amantadine, originally developed as an anti-viral to treat influenza, is now approved to treat PD patients with dyskinesias due to levodopa peak concentrations. The exact mechanism by which amantadine reduces levodopa-induced dyskinesia is unknown. However, glutamate is thought to play a role in dyskinesia, and amantadine is a weak antagonist of glutamatergic NMDA receptors.^{22,29} An ER formulation of amantadine is available as well. Patients take amantadine ER at bedtime, and it provides control of dyskinesia upon awakening and throughout the day.²² Possible side effects include nausea, constipation, dizziness, orthostatic hypotension, dry mouth, confusion, hallucinations, and peripheral edema. Pharmacists should be aware that very high doses can cause psychosis, particularly in elderly patients, and overdose can cause QT interval prolongation or Torsades de Pointes. Sudden amantadine withdrawal can cause exacerbation of PD symptoms, neuroleptic malignant syndrome, and acute delirium; pharmacists should counsel patients and caregivers on the importance of adherence to amantadine (see [Sidebar](#) above).²⁹

Figure 2. Medication management in the peri-DBS period³²



*adjunct medications include MAO-B inhibitors, COMT inhibitors, apomorphine, and amantadine

While novel drugs are being developed for PD, researchers also turn to drug repurposing—using existing drugs that have passed toxicity and safety tests for new indications. Tetracycline antibiotics, including doxycycline and minocycline, are thought to have neuroprotective effects in PD. They inhibit proinflammatory molecule production, matrix metalloproteinase activity, mitochondrial dysfunction, protein misfolding/aggregation, and microglial activation. Tetracyclines have excellent safety profiles and have been used for more than 50 years as antibiotics, making them excellent candidates for drug repurposing for PD.³¹

Surgical Treatment

Clinicians often suggest that patients with PD whose symptoms persist despite careful, appropriate medication management consider surgical options—either ablative surgery or deep brain stimulation (DBS). Ablative surgeries (pallidotomy, thalamotomy, and subthalamotomy) irreversibly destroy brain tissue in a precise region with a tiny heated probe. Pallidotomy is the most commonly employed of the three ablative procedures, and the benefits can be long-lasting.³² DBS involves the placement of leads—thin, platinum-iridium wires that have low corrosivity, high biocompatibility, and good mechanical resistance—into select regions of a patient’s brain. The surgeon connects these leads to a neurostimulator, a multi-programmable pacemaker-like device, which is implanted permanently in the chest below the collarbone, but can be removed surgically, if necessary. The device contains a battery and generates an electrical stimulus that is delivered to the brain via the lead(s). DBS is reversible through surgery and causes minimal damage to brain tissue. Providers can make adjustments to the system externally based on patient symptoms by “programming” the system.³²

Not every patient is a candidate for DBS; clinicians should select patients carefully. The best candidates tend to be younger (69 years or younger), but age is not the sole determining factor.

Good candidates have³²:

- Had symptoms for five years or more
- Experienced an appreciable response to PD medications (at least 30% improvement)
- Tried different combinations of PD medications
- Have intolerable symptoms that interfere with activities of daily living

As a general rule, if medication won’t help a PD symptom, neither will DBS. DBS most successfully addresses tremor, rigidity, and bradykinesia. DBS will also help with drug-induced motor complications, including dyskinesia, dystonia, and “on/off” fluctuations. Patients whose disabling symptoms are balance, walking, or speech are poor candidates for DBS. Most patients will remain on PD medications post-DBS, but many will substantially lower their daily doses. Rarely, a patient may be able to stop medications completely, but medication reduction or discontinuation should not be the goal. Symptom improvement and improved functioning with or without medication changes are the most important goals.³² Pharmacists can help set patient expectations regarding DBS and other surgeries and answer questions about whether the surgery may be appropriate for them. Pharmacists can also assist in medication management in the peri-DBS period, shown in [Figure 2](#).

Non-Pharmacologic Treatment

Exercise is an important component of healthy living for all people, but for PD patients it is even more critical. Exercise is

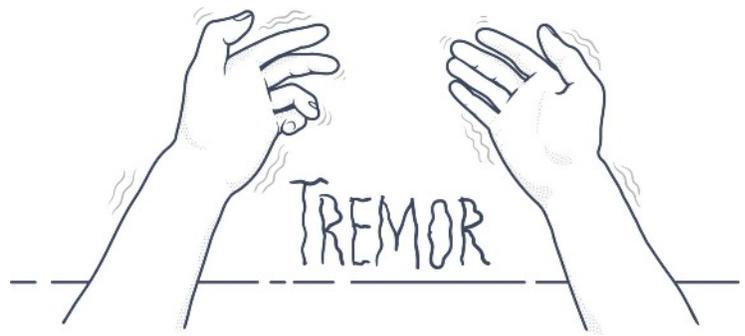
vital to maintaining balance, mobility, and activities of daily living. Physical activity can also improve NMS like depression and constipation. Studies show that PD patients who start exercising earlier at a minimum of 2.5 hours per week experience a slower decline in quality of life than those who start later and exercise less. Proper exercise routines for PD patients will address flexibility/stretching, aerobic activity, and resistance or strength training. Examples include biking, running, Tai chi, yoga, pilates, dance, weight training, and non-contact boxing. Patients in the early stages of PD are likely to be just as strong and physically fit as healthy people of the same age, but as PD progresses, patients experience physical changes that make exercise more of a challenge.³³ Pharmacists should encourage PD patients to exercise regularly, but only after consulting with their physician and/or neurologist first.

Maintaining a healthy diet is also important for PD treatment. Patients should drink plenty of water (six glasses per day) and eat fiber-rich foods (e.g. brown rice, whole grains, breads with 3 grams or more of dietary fiber per slice) to ease digestive difficulties and prevent constipation. Taking medications with a full glass of water may also help to break down medication more efficiently and improve efficacy. PD patients should limit sugar, alcohol, and caffeine intake especially close to bed time, as these substances can interrupt sleep. Pharmacists should also encourage PD patients to include the following in their diets³⁴:

- Walnuts, cashews, and other nuts to promote brain health
- Berries, which contain beneficial antioxidants
- Foods with anti-inflammatory effects on the brain, like salmon, tuna, and dark, leafy greens

In addition to the previously discussed drug interactions, some medications should be avoided in all PD patients³⁵:

- Typical and atypical antipsychotics block dopamine receptors in the brain, which worsens PD symptoms. If a dopamine-blocking antipsychotic must be used, however, the atypical class is preferred because they dissociate from the receptor faster than typical antipsychotics do.
- PD patients should also avoid taking antiemetics (drugs to treat nausea or vomiting) like chlorpromazine, metoclopramide, prochlorperazine, and promethazine. These drugs block dopamine receptors in the brain, worsening PD symptoms.
- Two antihypertensives should be avoided in PD patients; reserpine can decrease dopamine stores, and methyldopa inhibits an enzyme that converts levodopa to dopamine in the brain.
- Some antidepressants—phenelzine, tranylcypromine, and isocarboxazid—block MAO unselectively. This can result in dangerous spikes in blood pressure and agitation in patients on some PD medications
- Amoxapine, a tri-cyclic antidepressant, should also be avoided as it can also block dopamine receptors.



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NON-MOTOR SYMPTOMS

NMS are extremely frequent and important components of PD in all patients. Pharmacists should be familiar with these non-classic symptoms of PD and be sure that they are adequately addressed by providers.

Mood Changes

Depression is common in PD patients; about 17% of PD patients have major depressive disorder, 22% have minor depression, and 13% experience dysthymia (persistent depressive disorder). Depression can occur at any point in PD progression, and can even precede signs of motor dysfunction.³⁶ PD patients should be screened for depression at least once yearly, and pharmacists should recognize signs of depression in order to refer patients for treatment when appropriate³⁷:

- Persistent sadness, helplessness, or hopelessness
- Crying
- Loss of motivation or interest in usual hobbies and activities
- Decreased attention to hygiene and health needs
- Guilt, self-criticism, and worthlessness
- Increased fatigue
- Appetite changes
- Feelings of being a burden to loved ones
- Sleep difficulties
- Thoughts of death or suicide

A combination of counseling and medication is recommended to treat depression in PD patients. Most patients with depression are treated with selective serotonin reuptake inhibitors (SSRIs), including fluoxetine, sertraline, paroxetine, citalopram, and escitalopram. Others are treated with venlafaxine, mirtazapine, bupropion, or tricyclic antidepressants. SSRIs should be used with caution in patients taking MAO-B inhibitors for PD, as serotonin syndrome (accumulation of too much serotonin in the body, leading to fever, agitation, tremor, sweating, dilated pupils, and diarrhea) is possible. These antidepressants should be taken before 2 PM so they won't cause sleep disturbances, as some are activating.³⁷

About 25% to 40% of PD patients experience anxiety, most often

in the form of generalized anxiety disorder, panic disorder, or a phobic disorder (extreme fear or aversion). Anxiety often appears as a part of “wearing off” of medications.³⁶ SSRIs are commonly used for anxiety. Benzodiazepines— diazepam, lorazepam, clonazepam, and alprazolam—are another class of medications used to treat anxiety. They are very effective and work much faster than SSRIs. Unfortunately, benzodiazepines can also cause memory difficulty, confusion, balance problems, and tiredness, so they should be used with caution in PD patients and especially in elderly patients.³⁸

More than half of PD patients will eventually develop symptoms of PD psychosis, causing them to experience hallucinations and/or delusions. Hallucinations are when a patient sees, hears, experiences, or senses things that are not there. Delusions are false beliefs that are not based in reality. The cause of PD psychosis is unknown, but is thought to possibly be a side effect of dopamine therapy.³⁹ The only drug approved for PD psychosis is a newer atypical antipsychotic called pimavanserin. Pimavanserin does not block dopamine or worsen motor symptoms, and it can improve hallucinations, delusions, night-time sleep and daytime sleepiness. Side effects of pimavanserin include nausea, confusion and hallucinations.²²

Autonomic Dysfunction

Autonomic dysfunction can affect the entire autonomic nervous system (ANS) or a small part of the ANS, and causes dysregulation of nonvoluntary body functions (heart rate, blood pressure, sweating, etc.). Orthostatic hypotension—a drop in blood pressure that happens when standing up from sitting or lying down—affects up to 60% of PD patients. This drop can cause lightheadedness, fainting, and falls.³⁶ Droxidopa is a drug approved to treat orthostatic hypotension. While its mechanism in orthostatic hypotension is not totally understood, droxidopa is believed to exert its pharmacological effects through norepinephrine. Norepinephrine increases blood pressure by inducing peripheral arterial and venous vasoconstriction. Droxidopa should not be taken within three hours of bedtime, as it can cause a dangerous elevation of blood pressure while lying down. Other side effects include headache, dizziness, nausea, and fatigue.^{22,40}

GI dysfunction is also common; it can take the form of dysphagia (difficulty swallowing), gastroparesis (delayed gastric emptying), and constipation. Frequent dysphagia and inefficient swallowing can lead to drooling and even serious complications, like aspiration.³⁶ PD patients can also experience excess secretions (sweating, drooling). More than 50% of people with PD drool excessively, which causes skin breakdown around the mouth, odors, embarrassment, or choking. Incobotulinumtoxin-A is an injectable medication approved for chronic sialorrhea (excessive saliva production). A health-care provider injects the drug into the parotid and subman-

dibular glands on both sides of the face/neck every three to four months.^{22,41} PD patients with gastroparesis may experience early satiety, reduced appetite, bloating, nausea/vomiting, and weight loss. Impaired gastric emptying may also cause ineffective levodopa absorption, since the drug must reach the small intestine to be absorbed.³⁶ Providers should consider patients with gastroparesis for non-oral medication administration so it is better absorbed and more effective.

Sleep Disturbances & Daytime Sleepiness

The prevalence of disturbed or impaired sleep in PD is close to 90%.³⁶ The most common sleep issues in PD patients are⁴²

- Difficulty falling and staying asleep
- Talking or yelling out while asleep
- Vivid dreams
- Restless legs (jerking or cramping)
- Difficulty turning over in bed
- Waking up to use the bathroom
- Excessive daytime sleepiness

Proper sleep hygiene habits are the best way to combat sleep disturbances and daytime sleepiness in PD patients. Pharmacists should advise patients that consistency is key. They should keep a regular sleep schedule, planning to spend seven to eight hours a night in bed. If patients want to nap, they should do so at the same time every day, for no more than an hour and not after 3:00 PM. PD patients should also restrict fluid intake for three hours before bedtime and use the bathroom immediately before retiring to avoid frequent nighttime urination. If urinary frequency is a problem, pharmacists should advise patients to talk to their neurologist or see a urologist about possible medications to assist. Some antidepressants, like mirtazapine, can also help with sleep, while others—SSRIs—can make sleep symptoms worse.⁴²



Tech Talk: Point-of-Sale Red Flags⁴³

Pharmacy technicians are poised to recognize drug interactions at prescription point-of-sale. Patients often bring over-the-counter items to purchase alongside their prescribed PD medication, so technicians should know what products to watch for.

Sedating medications: Sedatives can cause memory and thinking issues. Avoid antihistamines, like diphenhydramine, that could be sedating and otherwise only use them for short courses.

Dextromethorphan: This cough suppressant could interact with MAO-B inhibitors (selegiline, rasagiline, and safinamide).

Combination products: Help patients to select products that only treat their actual symptoms, and be wary of multi-symptom products with many active ingredients. Read labels and offer prompt to patients:

- Saying, “Did you mean to buy two products with similar ingredients? It’s harmful to double-up similar ingredients,” can prevent an overdose.
- Saying, “Please remember that this medication has acetaminophen in it, so be careful if you’re taking acetaminophen for something else.” Tell them that the maximum dose of acetaminophen is 3 grams (two 325 mg tablets every four to six hours) for healthy adults.

St. John’s wort: This supplement can affect the metabolism of many prescription drugs, including MAO-B inhibitors, causing them to be less effective. It should also not be taken with other antidepressants, like SSRIs.

PHARMACY TEAM'S ROLE

Pharmacy teams should take an active role in caring for PD patients. PD’s motor and non-motor symptoms can be debilitating and the disease is progressive, so symptoms and medication regimens change constantly. Pharmacists can make a big difference. Pharmacy teams can help PD patients by:

1. Counseling on cornerstone medications and their side effects: PD treatment is complicated and patients have to gather enormous amounts of information at their neurology appointments. Take the time to be sure they understand the importance of their PD medications and possible side effects. When patients know what to expect from their medications, they are more likely to adhere to them and be comfortable taking them. They will have a better idea of when to come to you, or their neurologist, for increased symptoms or side effects that should not be ignored.

2. Acknowledging non-motor symptoms and reassurance that medication can help: The classic symptoms of PD are motor symptoms, but NMS needs early recognition. NMS have a vast impact on quality-of-life for PD patients and pharmacy teams should be sure they are adequately addressed. Reassure patients that medication and lifestyle changes, like sleep hygiene, can help immensely with NMS and make recommendations for relief where appropriate. Also, be aware of your patients’ demeanor and note any mood changes. Depression is incredibly common in PD patients and pharmacy teams are positioned to see these changes before other providers and make a difference.

3. Screening for medications that interact or aggravate Parkinson's disease: Drug utilization review is an important step in the pharmacy process that cannot be ignored. PD treatment relies on a delicate balance of dopamine receptor stimulation; too much or too little can cause increased motor and

There’s an App for That^{44,45}

Smartphone apps can be a useful tool for PD patients, especially those with earlier symptom onset who may be more tech savvy. Here are a few to recommend:

Medication trackers: Many apps track medication administration, some more in-depth than others. Use medication trackers to manage daily dosing schedules, set alarms for administration, and record when doses are taken. This virtual pill-box can be helpful to PD patients on many medications.

Futurity: “Futurity” is a new iPhone app that uses visual, audio, and vibratory cues to help PD patients overcome “freezing” episodes. The app uses augmented reality through the phone’s camera to place the image of a block, circle, or other object where the patient’s foot should land.

Informational apps: Applications like “Parkinson’s Central” and “Parkinson Home Exercises” can provide useful information to PD patients on-the-go. “Parkinson’s Central,” developed by the National Parkinson Foundation, provides information about diet, exercise, and medications, and can connect patients to local support groups. “Parkinson Home Exercises” provides detailed instructions on 50 at-home exercises that help PD patients improve common symptoms.

Brain training: “Peak-Brain Training” is an app developed by neuroscientists. It has 30 games designed to improve cognitive function, including memory, attention, and problem solving.

non-motor symptoms. Take the time to make PD patients aware of over-the-counter medications they should avoid and to review patient profiles for possible interactions or contraindications regularly. Also, encourage them to stick to one pharmacy or keep medication lists up-to-date at all pharmacies they use to avoid potential missed drug interactions.

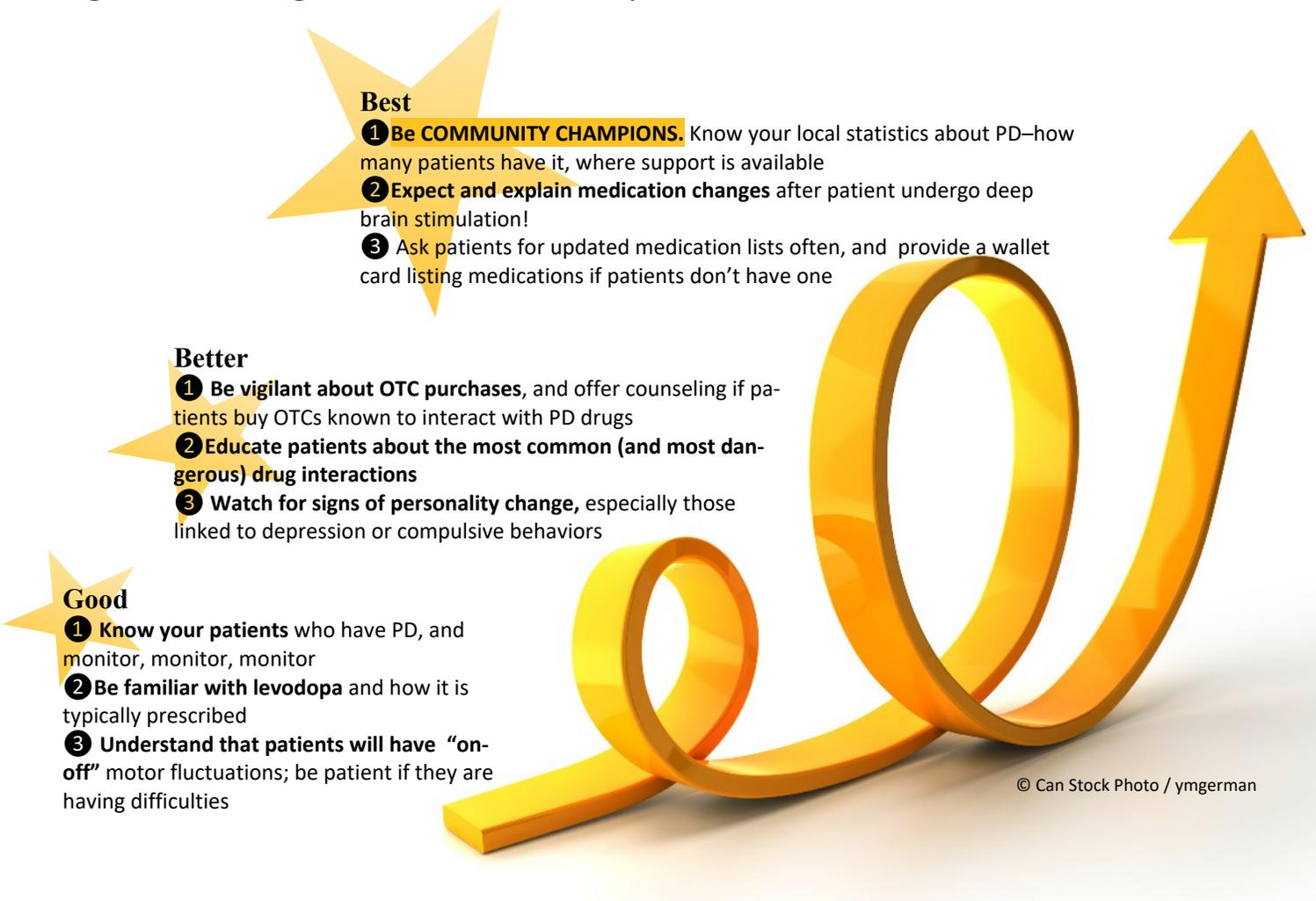
4. Helping patients step-up care: Opening the lines of communication with PD patients will make them more likely to be comfortable coming to the pharmacy team with questions or new symptoms. PD is a progressive disease, and you can act as a patient advocate when treatment appears to be inadequate. Offer to contact a patient’s provider for him or her when step-up appears necessary.

5. Counseling on medication adherence: Adherence to PD medications is crucial for proper symptom control. Encourage patients to use pill boxes to organize their multiple-daily dosing and to set alarms for administration times when appropriate. Pay attention to your PD patients’ refill histories; this can be a great way to track proper adherence. Also, as PD is a progressive disease, doses are adjusted often. Be sure to review dose changes with patients and use the teach-back method to ensure they understand.

CONCLUSION

PD is a progressive, debilitating disease. The classic motor symptoms are addressed frequently with medications, but oftentimes NMS can be overlooked. Adherence to PD medications is important. Pharmacy teams should take an active role in establishing a relationship with PD patients and ensuring their motor and non-motor symptoms are adequately addressed.

Figure 3. Advancing Pharmacists and Pharmacy Technicians Role in Parkinson’s Disease Care



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