EDUCATIONAL OBJECTIVES

GOAL: To assist pharmacists in managing difficult-to-treat symptoms of Parkinson’s disease

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
> Explain treatment approaches for depression, psychoses, and sleep disturbances in patients who have PD
> Outline the pharmacist’s role in assisting with adherence to PD therapy and symptom management overall and during the perioperative deep brain stimulation placement period

After participating in this activity, pharmacy technicians will be able to:
> Recall common symptoms of Parkinson’s disease (PD) and the typical medications used to treat them
> Identify typical and atypical problems associated with PD
> Recognize when to refer patients to the pharmacist for recommendations

The University of Connecticut School of Pharmacy is accredited by the Accreditation Council for Pharmacy Education as a provider of continuing pharmacy education.

Pharmacists and pharmacy technicians are eligible to participate in the knowledge-based activity, and will receive up to 0.2 CEUs (2 contact hours) for completing the activity, passing the quiz with a grade of 70% or better, and completing an online evaluation. Statements of credit are available via the CPE Monitor online system and your participation will be recorded with CPE Monitor within 72 hours of submission.

ACPE# 0009-9999-16-066-H01-P
ACPE# 0009-9999-16-066-H01-T

Grant funding: None

Activity Fee: There is no fee for this activity.

INITIAL RELEASE DATE: DECEMBER 10, 2016

EXPIRATION DATE: DECEMBER 10, 2018

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Key cogs in the management of Parkinson’s disease

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Abstract

Pharmacists play an important role in identifying the signs and symptoms of depression, psychosis, and insomnia in Parkinson’s disease (PD) and are an information source for patients, caregivers, and prescribers. Pharmacists also play an integral role in managing PD medication regimens in the time leading up to and after deep brain stimulation. Pharmacists are in a unique position to address nonadherence in PD patients, which can lead to poorly controlled disease and comorbid symptoms. Comorbid cognitive impairment or depression can heavily influence nonadherence, and pharmacists are on the front line of being able to identify symptoms and referring patients when appropriate. Recognizing symptoms and understanding when to refer a patient with these comorbid conditions is critical for patient safety and appropriate treatment.

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DISCLOSURE: Dr. Chamberlin and Ms. Sahbani have no actual or potential conflict of interest associated with this article.

DISCLOSURE OF DISCUSSIONS OF OFF-LABEL AND INVESTIGATIONAL USES OF DRUGS: This activity may contain discussion of unlabeled/unapproved use of drugs. The content and views presented in this educational program are those of the faculty and do not necessarily represent those of the Accreditation Council for Pharmacy Education.

Introduction

The apothecary and surgeon James Parkinson wrote of “paralysis agitans” in his publication “An Essay on the Shaking Palsy” in 1817. Parkinson’s disease (PD) is an incurable progressive movement disorder with a cardinal symptom of slowness of movement (bradykinesia) that also includes resting tremor, rigidity, and loss of postural reflexes. Dopamine replacement therapy substantially lessens motor handicap. Patients can also suffer from gait imbalance, pain, fatigue, depression, and sexual and cognitive changes. Its motor manifes-
tations, autonomic and neurologic disorders, and sensorial symptoms progress with disease worsening and create a high medication load for patients. Medication therapy management (MTM) has been shown to improve treatment effectiveness, safety, and convenience, and improve patients’ quality of life (QoL).

PD is generally a late-life disease that develops after age 60 years and increases in prevalence to 4% at age 80 years. Age is the main known risk factor for PD, although there appears to be some genetic predisposition. It is the 14th leading cause of death. In addition to the well-known primary, disease-modifying symptoms, PD patients almost always develop nonmotor symptoms (NMS) that are as distressing as the primary symptoms. NMS include sleep disorders, mood changes, cognitive impairment, blood-pressure fluctuation, and gastrointestinal disturbances. A 2016 needs assessment by the American Academy of Family Physicians identified that family physicians have a medical knowledge gap around diagnosing and managing the NMS of PD. Pharmacists play a critical role in bridging this gap with community-dwelling PD patients and their caregivers.

A 60-year-old man with Parkinson’s disease is struggling with depressive symptoms and his primary care physician wants a recommendation on the best pharmacologic therapy to use to treat him. What information might you obtain from him before making a recommendation?

**Degression in PD**

Depression is among the most common comorbid problems associated with PD, occurring in about 30% to 40% of patients. Due to the prevalence of PD-related depression, clinicians should screen all PD patients for this disease state. Diagnosis of depression in PD patients can be extremely difficult due to the overlap in symptoms; however, the symptom profile in PD patients is different than that in depressed patients with PD. Common indicators of depression in PD patients include anxiety, pessimism, irritability, irrationality, and suicidal ideation without a suicidal plan.

Therefore, it is imperative for physicians to utilize the proper screening tools when assessing their PD patients for depression. Although there is no specific scale to assess comorbid depression in PD patients, using appropriate cut-off scores of scales such as the Hamilton Depression Rating Scale and Beck Depression Inventory can be useful in evaluating PD patients for depression.

Despite the fact that a large number of PD patients suffer from depression, few controlled clinical trials have evaluated the safety and efficacy of pharmacologic treatment in this patient population. Most available data comes from the use of tricyclic antidepressants (TCAs) in PD patients with depression. Multiple studies have reviewed the use of nortriptyline and amitriptyline for PD depression and found that both are effective in relieving symptoms. A comparative study of low-dose amitriptyline and low-dose fluoxetine found that amitriptyline was the more effective of these drugs in controlling depression in PD patients, but higher dropout rates occurred among those on amitriptyline than among those on fluoxetine due to adverse events.

TCAs have shown efficacy in this patient population, but their adverse effects (eg, orthostatic hypotension, memory impairment, anticholinergic side effects) limit their use. Investigators have found that over 58% of PD patients experienced orthostatic hypotension, with a fall in systolic blood pressure of at least 20 mm Hg. A fall of more than 20 mm Hg in systolic blood pressure increases the risk of falls and syncope. Given that PD patients are prone to a fall in blood pressure, the added decrease from TCAs would be unwelcome. PD patients are also at increased risk for developing psychosis, which can be accelerated by the memory impairment that can arise from using TCAs. Although their anticholinergic effects can be limiting, anticholinergic agents are typically used in PD patients with tremor-dominant symptoms. Therefore, the anticholinergic effects of TCAs can be beneficial in these patients to control their motor symptoms as well as their depression.

Currently, insufficient evidence supports or refutes the effectiveness of antidepressants other than TCAs. Although TCAs are the most-studied antidepressant class in PD patients with depression, clinicians tend to choose selective serotonin reuptake inhibitors (SSRIs) as first-line agents largely because of a proven record of overall safety, toler-
Evidence from a randomized, placebo-controlled trial suggests that the dopamine agonist pramipexole improved depressive symptoms associated with PD and should be considered in the management of PD depression. Another study comparing pramipexole to sertraline concluded that pramipexole can be a potential alternative to antidepressants for PD patients. The adverse events noted within the trial are consistent with the known safety profile of the drug, including nausea, headache, dizziness, and somnolence.

In the absence of a gold standard treatment for PD depression, drug selection should be individualized for each patient, based on the potential advantages and disadvantages each agent provides.

**Psychosis in PD**

A population-based study of psychosis in PD patients found that psychosis occurs in over 50% of patients at some point over the course of the disease. Multiple studies have shown that psychosis is among the highest risk factors for admission to a nursing home, increased hospitalization costs, and increased mortality in PD patients. Symptoms of psychosis in PD patients include hallucinations, illusions, and delusional behavior. As symptoms of psychosis begin to arise, patients experience hallucinations with retained insight, which tends to degrade as the disease progresses. Patients who experience hallucinations with retained insight are aware that they are exhibiting psychological disturbances and are able to attribute it to their disease state. Prevalence of psychosis in PD patients increases with chronic use of dopaminergic agents, which are known to cause psychosis and commonly employed in the treatment of PD. Dopaminergic over-activity in the cerebral cortex and limbic system has been hypothesized to be involved in PD psychosis. Risk factors for PD psychosis include cognitive impairment, sleep disorders, longer duration of PD, and depression.

Although it is not FDA approved for this indication, clozapine is currently the gold standard treatment for PD psychosis. A landmark study used low-dose clozapine for the treatment of PD psychosis and found an improvement in symptoms. The study used clozapine doses between 6.25 mg/day and 50 mg/day, which is significantly lower than the doses used for schizophrenia (300–900 mg/day). In this range, clozapine reduced the severity of psychosis in PD patients. Of the antipsychotics, clozapine has been evaluated in PD patients for its low potential to exacerbate parkinsonism. Multiple randomized, clinical trials have demonstrated clozapine’s efficacy without worsening motor symptoms.

A retrospective analysis assessing the long-term use of clozapine for PD patients with psychosis has shown that clozapine maintains its safety and efficacy. The study found that of 39 patients evaluated, none discontinued clozapine due to motor worsening.

Although clozapine’s efficacy has been
demonstrated, physicians are hesitant to use it due to its potential for agranulocytosis and required, ongoing monitoring.\textsuperscript{34} Product labeling requires strict monitoring of clozapine in which the complete blood count (CBC) is monitored weekly for the first 6 months, biweekly for the next 6 months, and then monthly. If patients can tolerate the routine CBC monitoring, clozapine would be the treatment of choice. Despite the insufficient evidence on the efficacy of quetiapine in the treatment of PD psychosis, it is often used as a first-line treatment. When compared to placebo in a double-blind trial, quetiapine failed to exert a significant antipsychotic effect at doses up to 200 mg/day. This study did show, however, that quetiapine did not worsen parkinsonism.\textsuperscript{35} Other investigators conducted a small randomized, controlled trial comparing quetiapine up to doses of 150 mg/day versus placebo.\textsuperscript{36} Quetiapine failed to improve psychosis in PD patients, although the small sample size limits the ability for interpretation. An open-label trial compared quetiapine to clozapine and found that quetiapine was as effective as clozapine in reducing dopaminergic psychosis. This trial showed that clinical symptoms of hallucinations and delusions responded similarly to either agent.\textsuperscript{37} The results of this study demonstrated that quetiapine can be effective and well tolerated in this patient population; however, because this study contained a small sample size and was un-blinded, its validity is limited. Due to conflicting data among randomized clinical trials, quetiapine has been regarded as having “insufficient evidence, acceptable safety risk with- out need for specialized monitoring,” but investigational practice implications.\textsuperscript{38} Most clinicians have opted for quetiapine due to its ease of use, as it does not require routine CBC monitoring. Like clozapine, quetiapine has greater affinity to 5HT2 receptors than to dopaminergic receptors, which decreases the potential for worsening of motor function. Multiple studies have demonstrated that quetiapine improves symptoms and is generally well tolerated within goal dosing of 50 to 150 mg nightly.\textsuperscript{39,40} Other multiple studies have looked into the use of risperidone to alleviate psychotic symptoms in PD patients and have found that it worsens motor function.\textsuperscript{39,40} One study compared clozapine to risperidone and did not find a statistically significant difference in efficacy between the agents.\textsuperscript{41} However, both this study and

\begin{table}
\centering
\begin{tabular}{|l|l|l|l|l|}
\hline
\textbf{SLEEP DISTURBANCE} & \textbf{POSSIBLE CAUSE(S)} & \textbf{PHARMACOLOGIC INTERVENTIONS} & \textbf{NONPHARMACOLOGIC INTERVENTIONS} & \\
\hline
\textbf{Sleep onset} & Unknown Drug-related (activation) & \begin{itemize}
\item Hypnotics (short-acting, Z-class such as zolpidem, zaleplone, eszopiclone, amitriptyline)
\item Remove or reduce associated drug
\end{itemize} & Sleep hygiene:
- Regular sleep schedule (time of bed, time of awakening)
- Avoid alcohol and stimulants after 3 pm
- Comfortable, dark, quiet sleep environment
- Avoid consuming large amounts of food or liquids before bedtime
\textbf{Stimulus control}:
- Go to bed only when sleepy
- Minimize/avoid daytime napping
- Keep bedroom for sleep and intimacy only (not reading, TV, etc.)
- If difficulty sleeping, get out of bed and only return when sleepy
- Practice relaxation techniques (eg, meditation, muscle relaxation)
\hline
\textbf{Sleep maintenance} (including wake after sleep onset or early awakening) & Wear off, resting tremor, rigidity Drug-induced dyskinesia Depression, anxiety Nocturia & \begin{itemize}
\item Hypnotics (intermediate-type, such as temazepam; re-dose of short-acting, such as zolpidem IR)
\item Increase frequency of levodopa and reduce dose per administration; add dopamine agonist
\item Antidepressant (SSRI, SNRI, TCA); anxiolytics; dopamine-agonist
\item Urinary anticholinergics as appropriate (caution in patients with hallucinations and/or cognitive decline) (eg, oxybutynin; desmopressin nasal spray (monitor for nocturnal hypertension); dopamine agonist
\end{itemize} & \begin{itemize}
\item Remove/reduce dose of causative agent (eg, dopamine agonist)
\item Consider stimulant therapy (eg, caffeine, methylphenidate, modafinil)
\end{itemize}
\hline
\textbf{Excessive daytime sleepiness} & Drug-related Refractory & \begin{itemize}
\item Reduce dopaminergic drugs; consider atypical antipsychotics (quetiapine typically first choice; avoid risperidone)
\end{itemize} & \textbf{REM sleep behavior disorder} considerations:
- Remove hazards (objects in bedroom)
- Consider placing mattress on floor near bed
\hline
\textbf{Deliirium, delusion, hallucination} & NR & \begin{itemize}
\item Reduce dopaminergic drugs; consider atypical antipsychotics
\end{itemize} & Sleep apneas:
- Weight loss, as appropriate
\hline
\textbf{REM sleep behavior disorder} & NR & \begin{itemize}
\item Benzodiazepine (clonazepam first choice); melatonin; pramipexole in combination with clonazepam; some evidence with melatonin
\end{itemize} & \\
\hline
\textbf{Restless leg syndrome} (including periodic limb movement disorder) & PD treatment time of administration Anemia (serum ferritin <50 µg/L) & \begin{itemize}
\item Dopamine agonist scheduled before bedtime
\item Iron supplementation
\item Benzodiazepine (eg, clonazepam)
\end{itemize} & \\
\hline
\textbf{Sleep apneas} & NR & \begin{itemize}
\item CPAP: surgical intervention
\end{itemize} & \\
\hline
\end{tabular}
\caption{Sleep disorder management in Parkinson’s disease}
\end{table}

\textbf{Abbreviations:} CPAP, continuous positive airway pressure; IR, immediate release; NR, not reported; PD, Parkinson’s disease; REM, rapid eye movement; SNRI, serotonin-norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant. Source: Refs 61–63

\textbf{TABLE 1}
an open-label study of risperidone have reported worsening of parkinsonism.\textsuperscript{40}

Pimavanserin is the first drug that has been developed and FDA approved specifically for the treatment of PD psychosis. Pimavanserin is a 5-HT\textsubscript{2A} inverse agonist that has no clinically relevant affinity for other receptors, thus making it uniquely different in its effects from those of comparator agents. This agent does not exert an effect on dopaminergic receptors, which accounts for the parkinsonian side effects seen with other antipsychotic agents. Pimavanserin was granted breakthrough therapy status based on the results of a phase 3 study that has shown significant improvements in psychosis symptoms without worsening parkinsonism.\textsuperscript{40} Although this drug is well tolerated, associated adverse events seen within this trial included urinary tract infections and falls. An increase in QT interval not associated with cardiac adverse events seen with the use of pimavanserin has also been noted in some patients.\textsuperscript{40} The drug is categorized under the antipsychotic class and therefore bears the boxed warning of increased risk of death in elderly patients with dementia-related psychosis.\textsuperscript{43} Pimavanserin is typically dosed at 34 mg once daily (taken as 2 \(17\) mg tablets), unless the patient is concurrently taking a strong CYP3A4 inhibitor such as itraconazole, ketoconazole, clarithromycin, or indinavir, for which the dose should instead be initiated lower at 17 mg daily and maintained on this dose until the patient finishes the course of the CYP3A4 inhibitor.\textsuperscript{43}

**Sleep disturbances in PD**

SLEEPlessness is one of the biggest impacts on QoL, with sleep disorders occurring in upward of a third of PD patients.\textsuperscript{44,45} A Norwegian survey of 233 PD patients found that they may be more distressed by insomnia and depression than by motor disability. Many report inability to sleep at night accompanied by excessive sleepiness during the day, the latter of which is experienced by PD patients 3.3 times more frequently than the general population.\textsuperscript{46,47} PD patients also suffer from insomnia and restless legs syndrome. Rapid eye movement (REM) sleep disorder occurs in 25% to 40% of PD patients by 5 years from the time of diagnosis and increases to 40% to 65% of PD patients by the 10-year mark.\textsuperscript{48} REM sleep disorder results in symptoms that include disturbed sleep and flailing arm and leg movements during dreaming.\textsuperscript{49}

Dopamine agonists have been associated with excessive daytime sleepiness (EDS), and monoamine oxidase B (MAO-B) inhibitors have many adverse effects and may cause sleep disturbances.\textsuperscript{45} Levodopa, in combination with a peripheral decarboxylase inhibitor such as carbidopa, is the most-effective pharmacologic therapy for PD and can often attenuate motor symptoms as much as 20% to 70% in the first 3 months of therapy.\textsuperscript{2} Ergoline dopamine agonists (DA) indicated for PD include bromocriptine and cabergoline; however, their use has fallen out of favor due to their established risk of valvular and lung fibrosis.\textsuperscript{50,51} Nonergoline DA indicated for PD include amantadine, apomorphine, entacapone, pramipexole, ropinirole, rotigotine, and tolcapone, which when used alone in PD, do not provoke dyskinesias compared to levodopa.\textsuperscript{2,46,52} Although often used alone in younger-onset PD (age <55 years), the addition of levodopa to DA monotherapy is often required within 3 years of diagnosis.\textsuperscript{53} First identified with pramipexole, DA as a class are now known to cause somnolence and impulse control disorders, among other treatment-associated adverse effects.\textsuperscript{54,55}

MAO-B inhibitors used for PD, such as rasagiline and selegiline, provide mild symptomatic benefit with a simpler treatment regimen than levodopa by decreasing the rate of turnover of striatal dopamine and prolonging the action of dopamine in the brain.\textsuperscript{56,57} Simplicity in regimen is not without its disadvantages: adverse effects, however, as the class of MAO-B inhibitors are associated with orthostatic hypotension, hallucinations, anxiety, nausea, and sleep disturbances. Selegiline is a 5-mg tablet or capsule typically dosed once at breakfast and again at lunch, although an orally disintegrating tablet is also available that is administered only once daily and can be titrated from 1.25 mg daily up to 2.5 mg daily after 6 weeks based on clinical response and tolerability.\textsuperscript{58} A transdermal formulation of selegiline is available for the FDA-approved indication of depression, but not PD. Selegiline is a major CYP2B6 substrate and minor 1A2, 2A6, 2C8, 2D6, and 3A4. Clopidogrel, ticlopidine, and prasugrel are weak CYP2B6 inhibitors, whereas efavirenz and rifampin are moderate inducers. Selegiline weakly inhibits

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**TABLE 2**

**Mnemonic for Parkinson’s patients considering deep brain stimulation**

<table>
<thead>
<tr>
<th>D</th>
<th>Does not cure</th>
</tr>
</thead>
<tbody>
<tr>
<td>B</td>
<td>Bilateral DBS is often required to improve gait; although unilateral DBS can have effects on walking</td>
</tr>
<tr>
<td>S</td>
<td>Smooths on/off fluctuations</td>
</tr>
<tr>
<td>I</td>
<td>Improves tremor, bradykinesia, stiffness, and dyskinesia in many cases, but may not eliminate them</td>
</tr>
<tr>
<td>N</td>
<td>Never improves symptoms unresponsive to the patient’s best “on”</td>
</tr>
<tr>
<td>P</td>
<td>Programming visits occur many times in the first 6 months, and follow-ups as frequently as every 6 months after</td>
</tr>
<tr>
<td>D</td>
<td>Decreases medications in many, but not all</td>
</tr>
</tbody>
</table>

Note: “DBS in PD” mnemonic developed by researchers at the University of Florida McKnight Brain Institute, Gainesville, FL.

Abbreviations: DBS, deep brain stimulation; PD, Parkinson’s disease. Source: Adapted from Ref 69
Rasagiline is a newer MAO-B inhibitor than selegiline, dosed at 0.5 to 1 mg once daily as adjunctive therapy with levodopa or as 1 mg once-daily monotherapy. Rasagline is less likely to cause insomnia than selegiline. Rasagline is a major substrate of CYP1A2. Ciprofloxacin is a strong inhibitor of 1A2, and coadministration with rasagline should be avoided. Allopurinol, caffeine, famotidine, and verapamil are examples of weak 1A2 inhibitors that a PD patient may be taking.

Of note, EDS was found to be present in more than half of PD patients surveyed in 2000. The investigators used the Epworth Sleepiness Scale (ESS), a measure of the general level of sleepiness in adults, to evaluate PD patients for sudden-onset sleep while driving. Almost 4% of patients enrolled had sudden onset of sleep while driving. Interestingly, the authors were unable to identify specific anti-PD drugs or drug classes associated with daytime sleepiness and sleep attacks while driving. The authors concluded that sudden-onset sleep without warning is infrequent overall among PD patients taking DA. The ESS demonstrated sensitivity for predicting prior episodes of falling asleep while driving, and its specificity was shown to be increased when used in conjunction with the Inappropriate Sleep Composite Score. Investigators could not state for certain if routine assessment with these scales could effectively prevent future sleep attacks while driving.

A recent study examining MTM services for PD patients in a community pharmacy also looked at sleeping problems. Two pharmacists conducted MTM services and included 70 patients in the results, 51 of whom completed the expected 6 months of MTM. Demographers, pharmacotherapy, lifestyle, comorbidities, memory and cognition, PD symptoms, and QoL were reviewed in-person with patients in almost 74% of cases. Sleep disorder was identified as among the most frequent neurologic comorbidities, second only to depression (42.3% and 30.8%, respectively). The main interventions were performed directly with the patients, and involved nonpharmacologic and medication rescheduling methods to resolve sleeping problems. More than 71% of the recommendations were accepted, and all of them resolved the sleeping problems. Table 1 summarizes pharmacologic and nonpharmacologic sleep problem interventions.

### Deep brain stimulation for PD

Deep brain stimulation (DBS) is the most commonly performed reversible, minimally destructive surgery for PD in North America. More than 25% of current PD patients have a DBS device, at a cost between $35,000 and $50,000 for unilateral placement, and upward of $70,000 to $100,000 for bilateral procedures. Other surgical options are ablative, and targets include pallidotomy (globus pallidus), thalamotomy (thalamus), and subthalamotomy (subthalamus), all of which irreversibly destroy brain tissue in a precise region with a tiny heated probe. DBS involves the placement of a battery-operated electrode connected to an implantable pulse generator (IPG) similar to a pacemaker that delivers electrical current to a targeted area in the brain. Three primary targets for DBS influence nerve signals that cause tremor and other PD symptoms, including the ventral intermediate (VIM) nucleus of the thalamus, globus pallidus interna (GPI), and the subthalamic nucleus (STN). The device is then externally programmed, and adjustments to amplitude, frequency, and pulse width can be made. Patients have the ability to turn the device off as desired, but it is generally left on.
Candidates for DBS include those who are responsive to levodopa therapy, neuropsychiatrically intact (eg, no dementia), and have intractable dyskinesias, motor fluctuations, or tremor. Researchers at the University of Florida McKnight Brain Institute developed a mnemonic for PD patients considering DBS, "DBS IN PD" (Table 2).60 This mnemonic helps temper PD patient expectations to meaningful improvements when considering DBS, as opposed to the unrealistic expectations of dramatic improvement in PD symptoms not always attained.60 Generally, the best candidates tend to be younger (<69 years, but older age is not a contraindication), have had symptoms for at least 5 years, have experienced at least 30% improvement in symptoms from different combinations of PD medications with insufficient duration of effect, and have symptoms that are intolerable and interfering with daily functioning.70,71 If patients are still responding to medication, then DBS has the potential to affect PD symptoms. DBS will not work in patients who are nonresponders to standard PD medications.70

The 2006 National Institute for Health and Care Excellence (NICE) clinical guidelines for PD diagnosis and management give recommendations for best practice based on experience of the Guideline Development Group.72 This group suggests probe placement in 1 of the 3 target regions of the brain based on patient’s presentation. Table 3 describes which PD patient may have the best response to DBS placement in a given brain target.64,67,72,73 The Movement Disorder Society-Unified Parkinson’s disease rating scale (MDS-UPDRS) is the most commonly used scale to evaluate clinical progression of PD.74 The MDS-UPDRS includes nonmotor and motor experiences of daily living, motor examination, and motor complications that assist the practitioner in assessing the severity staging of PD. The assessments are typically conducted through interviews and observation and used to assess the patient longitudinally. Physicians use the MDS-UPDRS at baseline, when the patient is both on and off medication, to assess which symptoms will respond best to DBS.

Patients generally continue taking their PD medication regimen as prescribed until 12 hours prior to surgery. Patients will remain off medication for at least 12 hours after surgery. Remaining awake during the procedure leads to the best outcomes, as surgeons can accurately map and pinpoint locations that relieve specific PD symptomatology.67 Post surgery, the IPG is not immediately activated and patients typically must maintain their presurgery medication regimen. This limits acute dopaminergic withdrawal and malignant hyperthermia.75

Once the patient has recovered from surgery, external programming of the device can occur by a neurologist in the outpatient setting. Because STN-DBS can be synergistic with levodopa (STN stimulation can make levodopa more effective), medication reductions can occur while methodically ramping up DBS currents.76 Medication dose reduction in these patients can significantly lower side effects such as dyskinesias typically caused by levodopa exposure.67 Patients who have GPI- and VIM-DBS do not typically incur medication regimen changes post implantation due to lack of identified synergy with the probe placement and standard PD therapies. These non-STN-DBS patients can typically have implant intensity ramped more quickly due to the lack of drug synergy. Non-levodopa adjunctive therapies are typically dose-reduced first, with levodopa and dopaminergic-agonist therapies addressed subsequently. Most medication adjustments are achieved during the first month after surgery.77 A simple goal of reducing or completely relieving motor fluctuations and dyskinesias can be considered optimal treatment in many DBS patients.78

DBS is not without risks, with the highest likelihood of complications occurring in the first weeks post implantation. Infection, cranial bleeding, and seizure are the most common postsurgical complications.78 Infection is the most common surgical complication with DBS, with rates varying between 0% and 15% per patient and 0% and 9.7% per electrode.71 Most studies identify the highest risk of infection to be within the first month after surgery. Intracranial hemorrhage (both symptomatic and asymptomatic) is relatively low, rates ranging between 0% and 4.5% overall, but patients have poorer outcomes and longer hospital stays.71 Seizure rates are relatively low in postsurgical DBS patients, with reported incidences between 0% and 4% and the overall risk of developing epilepsy close to 0%.71 Long-term complications often include hardware discomfort (1.1%) and loss of desired effect (1.4%). Hardware discomfort that required surgical revision has included wound infections (1.7%), lead misplacement or movement (1.7%), device malfunction or wire fracture (1.9%), and loss of effect (2.6%).79 The American Academy of Neurology reported a death rate in DBS surgery patients of 0.6%.84

Pharmacist’s role
Pharmacists may improve care for patients with PD if they integrate current evidence-based guidelines and recommendations into their daily practice. Guidelines that are used widely and well-respected include:

- National Institute for Health and Care Excellence (NICE) Parkinson’s disease in over 20s Clinical Guideline (CG35)72
- The American Academy of Neurology...
(ANN) Practice Parameter: Treatment of Nonmotor Symptoms of Parkinson Disease

Pharmacists need to watch for another common problem. Nonadherence is frequent among PD patients, ranging from 33% to 73% in most studies. Much like adherence in HIV/AIDS, adherence in PD is profoundly influenced by the patient’s emotional readiness to initiate pharmacologic therapy and expectations before initiating antiparkinsonian medications. This calls for much support and motivational interviewing. The symptoms of PD patients are highly individualized, and their nonadherence reflects the magnitude and types of symptoms they experience. The most common type of nonadherence in PD patients is timing nonadherence. The cause is multiple daily medication doses and self-adjustment to handle fluctuating symptoms.81 Comorbid cognitive impairment or depression heavily influences nonadherence, and failure to address them creates a progressive cycle of poorly controlled disease, increasing depression, and spiraling uncontrolled symptoms. Psychosis clearly affects adherence, creating the need to involve a caregiver. Because most PD patients are older, their status with Medicare and their Medicare Part D plans are also financial factors that can be barriers.81 Clinicians and pharmacists can educate patients that DBS can make medication cessation possible, but likely not probable.79

Pharmacists who have patients in their caseload who consider or undergo the DBS procedure need to know that DBS helps improve PD’s motor symptoms, but will not tackle symptoms unresponsive to medication. Medication changes are needed before surgery, immediately after surgery, and in the weeks and months thereafter. Although most patients still need to take medication after undergoing DBS, many patients experience considerable reduction of their PD symptoms and are able to greatly reduce their medications. The amount of reduction varies from patient to patient but can be considerably reduced in most patients.87

Conclusion

Pharmacists are often the most-accessible healthcare provider for many patients and caregivers, including those with Parkinson’s disease. Pharmacists can offer insight, referrals, and recommendations to interprofessional team members for optimal management of parkinsonian disease- and treatment-related symptoms and adverse effects. The ability to recognize when symptoms persist or worsen and to refer these patients for further medical intervention is paramount to patient safety.

References are available online at www.drugtopics.com/cpe. 

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**TEST QUESTIONS**

**FOR PHARMACISTS**

1. Which of the following is not a “best” characteristic of a Parkinson’s disease (PD) patient when considering deep brain stimulation (DBS)?
   - a. Symptoms for 2 years
   - b. Age <69 years
   - c. Short duration of effect from PD therapies
   - d. Intolerable symptoms interfering with daily functioning

2. The highest risk of complications following DBS implantation occurs after surgery in the first:
   - a. Hours
   - b. Weeks
   - c. Months
   - d. Years

3. Most medication adjustments are achieved during which time period following DBS implantation?
   - a. First few days
   - b. First few weeks
   - c. First month
   - d. First year

4. Which of the following complications of DBS implantation typically occur in the first month or so following surgery?
   - a. Hardware discomfort
   - b. Loss of desired effect
   - c. Device malfunction
   - d. Intracranial hemorrhage

5. Patients receiving GPI-DBS and VIM-DBS typically may have which of the following medication changes to their original levodopa regimen?
   - a. No change
   - b. Levodopa dose lowering
   - c. Levodopa dose increase
   - d. These patients are not typically on levodopa therapy

6. Which of the following sleep disorder symptoms is not a symptom that necessarily occurs more frequently in PD patients?
   - a. Sleep apneas
   - b. Flailing leg movements
   - c. Flailing arm movements
   - d. Daytime sleepiness

7. Which of the following MAO-B inhibitors approved for PD causes the least insomnia?
   - a. Selegiline
   - b. Rasagiline
   - c. Phentolamine
   - d. Tranylcypromine

8. In patients experiencing excessive daytime sleepiness, medication interventions can include:
   - a. Dose reduction of the dopamine agonist
   - b. Dose reduction of the levodopa
   - c. Consideration of add-on stimulant therapy
   - d. A and C

9. STN-DBS placement patients may:
   - a. Experience synergy with levodopa
   - b. Have slower intensity ramping

CONTINUED ON PAGE 62
TEST QUESTIONS

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10. Good sleep hygiene techniques to educate PD patients about include:
   a. Regular sleep times
   b. Avoiding alcohol and stimulants early in the day
   c. Consuming large amounts of fluids or food before bedtime
   d. Reading in bed

11. Pimavanserin has the highest affinity for which receptor?
   a. 5HT2C
   b. 5HT2A
   c. D1
   d. D2

12. Which of the following is frequently monitored if a patient is placed on clozapine?
   a. Chemistry panel
   b. Clozapine levels
   c. Complete blood count
   d. All of the above

13. All of the following have shown safety in Parkinson’s patients with psychosis except:
   a. Risperidone
   b. Clozapine
   c. Aripiprazole
   d. A and C

14. Pimavanserin is labeled with a boxed warning for:
   a. QT prolongation
   b. Agranulocytosis
   c. Dementia in elderly patients
   d. Does not have boxed warning

15. Which of the following are risk factors for PD psychosis?
   a. Insomnia
   b. Depression
   c. Chronic use of dopaminergic agents
   d. All of the above

16. Which of the following is an antiparkinsonian that is also beneficial for depression?
   a. Berotropine
   b. Levodopa
   c. Sertraline
   d. Pramipexole

17. Which of the following has been associated with orthostatic hypotension in PD patients?
   a. Sertraline
   b. Amtriptyline
   c. Fluoxetine
   d. Paroxetine

18. A limiting side effect of sertraline for this patient population can be:
   a. Orthostatic hypotension
   b. Memory impairment
   c. Sexual dysfunction
   d. Hallucinations

19. A patient is taking selegiline as part of her PD regimen and the primary care physician would like to add something for depression. Which of the following is the best choice?
   a. Nortriptyline
   b. Amtriptyline
   c. Sertraline
   d. Pramipexole

20. Which of the following has shown the most efficacy in PD depression?
   a. Sertraline
   b. Fluoxetine
   c. Paroxetine controlled release
   d. Citalopram

FOR PHARMACY TECHNICIANS

1. Selegiline is available for the treatment of Parkinson’s disease (PD) in which of the following formulations?
   a. Vial
   b. Patch
   c. Syrup and patch
   d. Capsule and orally disintegrating tablet

2. Which of the following medications can have a major drug–drug interaction with rasagiline?
   a. Aspirin
   b. Ciprofloxacin
   c. Omeprazole
   d. Levofoxacin

3. Which of the following MAO-B inhibitors approved for PD causes the least insomnia?
   a. Selegiline
   b. Rasagiline
   c. Phenelzine
   d. Tranylcypromine

4. Parkinson’s patients undergoing deep brain stimulation (DBS) implant surgery will typically need to stop their PD therapies:
   a. 6 hours prior to surgery
   b. 8 hours prior to surgery
   c. 12 hours prior to surgery
   d. They do not need to stop their medications prior to surgery.

5. Patients receiving a STN-DBS implant might typically have the following changes to their original levodopa therapy:
   a. Dose increase
   b. Dose reduction
   c. Dose maintained
   d. Levodopa is usually able to be discontinued

6. A patient brings in a prescription for pimavanserin, and you see in his profile that he has been taking indinavir. Which dose of pimavanserin is appropriate for this patient?
   a. 34 mg once daily
   b. 17 mg once daily
   c. 17 mg twice daily
   d. Do not fill pimavanserin

7. A patient has recently started clozapine and has been stable for 7 months. How often should her CBC be monitored?
   a. Every 6 months
   b. Monthly
   c. Biweekly
   d. Weekly

8. Psychosis increases all of the following except?
   a. Risk for admission into nursing homes
   b. Hospitalization costs
   c. Mortality
   d. Worsening motor function

9. Depression occurs in what % of Parkinson’s patients?
   a. 40%
   b. 51%
   c. 58%
   d. 20%

10. The gold standard for treatment of depression in PD is:
    a. Sertraline
    b. Nortriptyline
    c. Amitriptyline
    d. None of the above

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