Parkinson Disease

Presenter: Dr. Milta Little
Disclosure Statement: I have nothing to disclose.

Objectives: By the end of the session, participants will be able to…

- Describe the clinical features of Parkinson Disease (PD)
- Identify "red flag" symptoms that would suggest an alternate diagnosis to PD
- List the treatments used to treat the motor and non-motor symptoms of PD

Expected Outcomes (Desired change in practice):

- Distinguish PD from other Parkinsonian conditions
- Follow a step-wise approach to symptom management to maximize functional status

Article for Review:

- Reich SG and Savitt JM. Parkinson's Disease. Med Clin N Am 103 (2019) 337–350

Outline for Rapid Fire session

1. Case presentation: PD

   Mr. Nuro is a 68 y/o cis-gender male with h/o HTN, CAD, DM, peripheral neuropathy, and CKD stage 3B who is admitted for post-acute care following a hospitalization for a fall from a step ladder leading to a non-displaced C1 fracture. He was treated non-operatively with a rigid collar immobilizer. During your interview, his wife reports that she has noticed over the last couple of years that he seems stiffer and that this has progressed to shuffling his feet and stooped posture. She states that it takes him twice as long to dress now as it did before, even before his fall and injury. You notice that his right hand is shaking and you ask about it. He and his wife state that it has been there for about a year but since he has several family members with tremors, they assume it runs in the family. Mr. Nuro states that his inability to move normally has been bothering him and he wants something to avoid further falls and decline. What else do you want to know? What are your next steps in working up his symptoms? What treatments might you offer?

2. Parkinsonism as a clinical syndrome
3. 4 steps in the diagnosis of PD
    a. Establish the presence of parkinsonism
    b. Identify features supportive of PD
    c. Identify absolute exclusion criteria
    d. Search for "red flags" that cast doubt on the diagnosis of PD

4. Parkinsonian syndromes
5. Treatment of PD

Parkinson's Disease

Stephen G. Reich, MD*, Joseph M. Savitt, MD, PhD

KEYWORDS

• Parkinsonism • Parkinson's disease • Tremor • Levodopa • Dyskinesias
• REM sleep behavioral disorder

KEY POINTS

- The diagnosis of Parkinson's disease (PD) is based on the presence of bradykinesia and either resting tremor or rigidity and the absence of features from the history or examination suggesting an alternative cause of parkinsonism.
- Alternative causes of parkinsonism include drug-induced parkinsonism and parkinsonian syndromes such as multiple system atrophy or progressive supranuclear palsy.
- Although PD is usually considered a purely motor disorder, there is a long list of nonmotor manifestations that are equally, if not more, disabling and significantly affect quality of life. Many of them precede the onset of motor symptoms, such as hyposmia and a rapid eye movement sleep behavioral disorder.
- Levodopa remains the mainstay of treatment for PD.
- For patients with PD with drug-resistant tremor or problematic motor fluctuations including dyskinesias, which cannot be medically managed, deep brain stimulation should be considered.

INTRODUCTION

Parkinson's disease (PD) is the second most common neurodegenerative disorder after Alzheimer disease. Although most patients are managed by neurologists, PD presents initially to the primary care physician who should be able to make the diagnosis, which is based on the history and physical examination. The term "parkinsonism" refers to a clinical syndrome, including bradykinesia, cogwheel rigidity, resting tremor, a slow shuffling gait, and imbalance. The most common cause of parkinsonism is PD but there is a lengthy differential diagnosis and the challenge is to determine if the patient has PD or another cause of parkinsonism such as drug-induced or a parkinsonian syndrome, such as multiple system atrophy (MSA, formerly Shy–Drager syndrome). In addition to the cardinal motor signs of PD, there is a broad array of nonmotor features,

Disclosure: None.
Department of Neurology, University of Maryland School of Medicine, 110 South Paca Street, 3rd Floor, Baltimore, MD 21201, USA
* Corresponding author.
E-mail address: sreich@som.umaryland.edu

Med Clin N Am 103 (2019) 337–350
https://doi.org/10.1016/j.mcna.2018.10.014 **medical.theclinics.com**
0025-7125/19/© 2018 Elsevier Inc. All rights reserved.

Downloaded for Anonymous User (n/a) at Duke University from ClinicalKey.com by Elsevier on February 07, 2022.
For personal use only. No other uses without permission. Copyright ©2022. Elsevier Inc. All rights reserved.

which for many patients are equally if not more disabling, such as orthostatic hypotension, dream enactment (a rapid eye movement (REM) sleep behavioral disorder [RBD]), or hallucinations. Because of space limitations, the nonmotor features will not be covered in detail. The diagnosis of PD and the available medical and nonmedical therapies to treat the motor features are reviewed in this article.

Parkinsonism

PD was described by James Parkinson's, a general practitioner in London, just over 2 centuries ago, in 1817. His succinct description is still applicable:

> *Involuntary tremulous motion, with lessened muscular power, in parts not in action and even when supported; with a propensity to bend the trunk forwards, and to pass from a walking to a running pace.*[1]

There have been tremendous advances in our understanding of PD since 1817,[2] more than can be covered here, and the authors focus instead on practical clinical aspects of diagnosis and management. In brief, PD is characterized pathologically by degeneration of dopaminergic neurons in the substantia nigra of the midbrain, leading to pathophysiologic changes in the circuitry of the downstream basal ganglia.[3] The Lewy body is the cytologic hallmark of PD and contains misfolded α-synuclein, the same protein that also accumulates in related disorders including multiple system atrophy and dementia with Lewy bodies, collectively referred to as "synucleinopathies."[4] Although a small percentage of patients with PD have a monogenetic cause, either dominant or recessively inherited (such as the genes LRRK2 or *parkin*, among others) most cases are sporadic and of unknown cause.[5]

Consider the following patient:

> A 60-year-old man complains of tremor of the dominant right hand for the past 6 months. All fine motor tasks with his right hand are more difficult such as brushing his teeth, turning pages, and texting. His handwriting has become smaller. He tends to scuff the right foot and has trouble sliding the right foot into a loafer. His wife has noticed that he does not swing the right arm while walking and that his voice is softer. Although not appreciated until asked, he acknowledges that his sense of smell has diminished. There is a history of constipation. When asked about sleep, his wife reports that for the past 10 years he has occasionally acted out a dream, appearing to be fighting, and during one episode he struck her during his sleep. Although he always was mildly anxious, this worsened recently with irritability and insomnia. On examination, there is decreased facial expression and his voice is mildly soft with diminished volume. There is a tremor at rest of the right hand. He has no difficulty arising from the chair. He walks a little slowly; the right arm does not swing, and the right shoe scuffs the floor, which can be both seen and heard. His posture is mildly flexed. He does not lose his balance when given a sudden pull backwards. His handwriting starts off normally but gets smaller toward the end of a sentence. Rapid repetitive movements of the right limbs are mildly slow but normal on the left. Strength is normal as are reflexes. When the right arm is passively moved, there is mild rigidity. Shoulder shrug is slower on the right.

Does this patient have PD? To answer this question, it is appropriate to evaluate this case using the diagnostic criteria for PD proposed by the Movement Disorder Society (MDS) (please refer to the criteria for a complete discussion).[6] There are 4 steps in the diagnosis of PD (**Box 1**); the first is to ensure the patient actually has parkinsonism. This is defined by the presence of bradykinesia and either a resting tremor or rigidity

Downloaded for Anonymous User (n/a) at Duke University from ClinicalKey.com by Elsevier on February 07, 2022.
For personal use only. No other uses without permission. Copyright ©2022. Elsevier Inc. All rights reserved.

Box 1
Four-step approach to the diagnosis of Parkinson's disease

Step 1: Establish the presence of parkinsonism
- Bradykinesia plus
- Rest tremor OR
- Rigidity

Step 2: Identify features supporting the diagnosis of PD
- Unequivocal and dramatic response to levodopa
- Presence of resting tremor
- Olfactory loss
- Other

Step 3: There should be no absolute exclusion criteria
- Cerebellar signs
- Supranuclear vertical ophthalmoplegia
- Treatment of dopamine receptor blocker or depletor within the past year
- Cortical sensory signs (agraphesthesia, astereognosis)
- Normal functional imaging of the presynaptic dopamine receptor
- Other

Step 4: Search for red flags that cast doubt on the diagnosis of PD
- Rapid progression (use of a wheelchair within 5 years of symptom onset)
- Early falls
- Early and severe dysarthria and dysphagia
- Early autonomic failure
- Bilateral, symmetric parkinsonism
- Absence of some of the nonmotor features expected with PD: RBD, hyposmia, constipation, anxiety, depression

Adapted from Postuma RB, Berg D, Stern M, et al. MDS clinical diagnostic criteria for Parkinson's disease. Mov Disord 2015;30(12):1595; with permission.

(note that about one-third of patients with PD do not have tremor). Bradykinesia is characterized by a combination of slowness of movement along with a reduction in the speed or amplitude of sustained repetitive movements (finger, hand, toe, or heel tapping). Tremor is best observed with the hands resting in the lap and sometimes can be brought out by mental distraction such as saying the months of the year backwards. A PD tremor often involves the lower extremity and may begin the foot. The tremor, like other signs of early PD, typically begins unilaterally and this is an important distinction with essential tremor (ET). Rigidity is perceived as a "lead-pipe" resistance to passive movement of the limbs and is best appreciated at the elbow or wrist. Based on these criteria, the abovementioned patient has parkinsonism.

The next step refers to "supportive criteria," that is, features that are typical of PD and usually not seen in other causes of parkinsonism. The most important of these is a "clear and dramatic beneficial response to dopaminergic therapy." Because this patient is not yet on dopaminergic therapy, this criterion cannot be fulfilled at this time, but eventually all patients with PD will require such treatment and until that time, the diagnosis of PD cannot be made with certainty. Additional supportive criteria include a resting tremor (which he has), and olfactory loss, which is also present and will be discussed later as a "prodromal" sign of PD. Although not part of the MDS supportive criteria, PD typically begins unilaterally, unrelated to handedness, and this is considered as an important supportive feature recognizing that no single clinical feature is free of false positives or negatives. Based on this, with the exception of an unknown response to dopaminergic therapy, this patient has other supportive features of PD.

Downloaded for Anonymous User (n/a) at Duke University from ClinicalKey.com by Elsevier on February 07, 2022.
For personal use only. No other uses without permission. Copyright ©2022. Elsevier Inc. All rights reserved.

The third criterion is the presence of features that are not expected with PD and point toward an alternative diagnosis. Only several will be discussed here and among them, one of the most important is the lack of exposure to a dopamine blocking or depleting medication in a time frame that could cause parkinsonism, and this typically means within the past year. Dopamine receptor blocking agents include all of the first-generation and many of the second-generation antipsychotics as well as metoclopramide. Because drug-induced parkinsonism may take as long as 1 year to resolve, the patient may no longer be on the offending drug at presentation and therefore it is essential to include this when taking a history. Other "absolute exclusion criteria" include lack of response to dopaminergic therapy, cerebellar signs, cortical sensory loss (agraphesthesia, astereognosis, extinction to double simultaneous stimulation), which suggest corticobasal syndrome, or restriction of vertical gaze, suggesting progressive supranuclear palsy. As will be discussed later, if functional imaging of the presynaptic dopamine transporter (DaTScan) is performed as part of the assessment of parkinsonism, and found to be normal, then that is also considered exclusionary for the diagnosis of PD. But, the criteria do not require such imaging and it is usually not necessary.

The final set of criteria are "red flags," which refer to features from the history and examination that do not necessarily reach the level of being an exclusionary feature for PD, yet do cast doubt on the diagnosis particularly when there are several.[7] They generally point toward a parkinsonian syndrome, which will be discussed later. Among several others, these include rapid progression of gait dysfunction, typically necessitating a wheelchair within 5 years of onset of symptoms; severe and early autonomic failure; early bulbar dysfunction such as severe dysarthria or dysphagia, both of which occur in PD, but not early in the course. Similarly, falls are common in PD but only seen in the middle to advanced stages and if present at onset or early in the course, suggest an alternative diagnosis such as MSA or progressive supranuclear palsy (PSP). Earlier it was mentioned that PD typically begins as hemiparkinsonism and as such, bilateral, symmetric parkinsonism should be considered a red flag. Although these criteria accept the presence of dementia at any time in the course of parkinsonism to be in keeping with possible PD, in the authors' opinion and experience, when dementia occurs early in the course of parkinsonism, and especially when it precedes it, this usually suggests an alternative diagnosis such as dementia with Lewy bodies.[8]

In contrast to all other red flags, which refer to the presence of a feature atypical for PD, the absence of certain nonmotor features expected in PD should also make one question the diagnosis. These include the lack of mild dysautonomia (constipation, erectile dysfunction, urinary urgency), the absence of an RBD (dream enactment), normal olfaction, and the lack of psychological features usually seen in PD such as depression and anxiety. The abovementioned patient does not have any exclusionary criteria nor are there any red flags. He has some of the expected nonmotor (premotor) features of PD, including constipation, recent exacerbation of anxiety, and an RBD all pointing to PD as the cause of parkinsonism. Even though the diagnosis of PD seems secure at this time, it is only during long-term follow-up that one is able to be more confident of the diagnosis because red flags may appear later in the course, and it remains to be determined if the patient will respond to levodopa and if so, will he eventually demonstrate fluctuations and dyskinesias that are expected with PD and not with alternative causes of PD. As such, it is important to continually reassess the diagnosis of PD at each visit. Ideally, all patients with parkinsonism should be referred to a neurologist to confirm the diagnosis. **Box 2** lists some additional features that can be helpful in the diagnosis of PD.

Downloaded for Anonymous User (n/a) at Duke University from ClinicalKey.com by Elsevier on February 07, 2022.
For personal use only. No other uses without permission. Copyright ©2022. Elsevier Inc. All rights reserved.

Box 2
Some tips for diagnosing Parkinson's disease

- The MDS criteria for PD[6] includes a very useful "completion form" providing a step-by-step checklist through the diagnostic process.
- Be sure to ask about a history of antidopaminergic therapy during the prior year.
- Early PD begins unilaterally, unrelated to handedness.
- Tremor is the most common presenting symptom of PD but one-third of patients do not have tremor and present with unilateral slowness or mild incoordination sometimes sensed as "weakness."
- PD may begin with tremor of the foot.
- The tremor of PD is often present when the patient is walking.
- Whether it begins in the upper or lower extremity, testing rapid repetitive movements will confirm that both limbs on the same side are affected.
- Shoulder shrug is slower on the symptomatic side.
- The resting tremor may "reemerge" while maintaining posture.
- The tremor of PD often involves the chin, tongue, lips, or jaw but typically not the head or voice.
- A handwriting sample is one of the best ways to distinguish PD from ET, assuming that PD involves the dominant hand.
- Refer to the text and the MDS criteria[6] for a list of red flags that cast doubt on the diagnosis of PD.
- Reconsider the diagnosis of PD at each visit because up to 20% of patients will prove to have an alternative cause of parkinsonism, typically a parkinsonian syndrome.
- Be familiar with the nonmotor features of PD because they assist in the diagnosis, are often overlooked, and are important determinants of quality of life.
- Although imbalance is one of the cardinal features of PD, it is not present early in the disease and if so, especially if accompanied by falls, suggests a parkinsonian syndrome.

PARKINSONIAN SYNDROMES

Even though the diagnosis of PD is considered straightforward, often termed a "waiting room diagnosis," autopsy studies have demonstrated that 20% of patients diagnosed with PD during life have an alternative diagnosis at autopsy.[9] The most common mimickers are parkinsonian syndromes—that is, other neurodegenerative disorders that share some features with PD but are distinct in terms of having clinical signs not usually seen with PD (red flags) and demonstrating little or no response to levodopa or the rapid waning of an initially beneficial response. These syndromes are more rapidly progressive and debilitating than PD, with patients usually dying within a decade of onset.

Multiple system atrophy is characterized by the presence of autonomic failure accompanied by either parkinsonism, which is unresponsive to levodopa (MSA-P), or cerebellar ataxia (MSA-C).[10,11] MSA has replaced the prior diagnoses of Shy–Drager syndrome, olivopontocerebellar atrophy (OPCA), and striatonigral degeneration because it was ultimately recognized that they were different presentations of the same disorder. Dementia with Lewy bodies, as MSA, is a synucleinopathy.[12] It is characterized by the presence of dementia either preceding (typically within 2 years) or appearing concurrent with parkinsonism. As mentioned earlier, the authors

Downloaded for Anonymous User (n/a) at Duke University from ClinicalKey.com by Elsevier on February 07, 2022.
For personal use only. No other uses without permission. Copyright ©2022. Elsevier Inc. All rights reserved.

consider early dementia in the setting of parkinsonism as a red flag pointing away from PD. Other characteristic features of dementia with Lewy bodies include fluctuations in mental status, which are otherwise unexplained; visual hallucinations unrelated to medication; RBD; and sensitivity to dopamine receptor blocking agents.

The other broad category of parkinsonian syndromes is known as tauopathies, in contrast to synucleinopathies, referring to the accumulation of abnormally phosphorylated tau in specific brain regions. PSP[13,14] is characterized by early falls, axial parkinsonian signs (stiffness and slowness), frontal-executive dysfunction, and slow vertical saccades (saccades are the eye movements that shift gaze between targets), eventually leading to restricted vertical eye movements (supranuclear vertical ophthalmoplegia). This is the classic form of PSP, also known as Richardson syndrome but it has a heterogeneous clinical picture and may also manifest as freezing of gait, nonfluent aphasia, or frontotemporal dementia. Corticobasal degeneration[15] is related to PSP but much less common and typically presents with a combination of cortical signs (agraphesthesia, astereognosis, aphasia, myoclonus) and basal ganglia signs such as dystonia, rigidity, or a "useless" limb. Corticobasal degeneration typically presents unilaterally, as does PD, whereas most of the other parkinsonian syndromes begin symmetrically.

Although not a parkinsonian syndrome, parkinsonism is often attributed to cerebrovascular disease. This is usually considered in the patient with disproportionate parkinsonian signs from the waist down ("lower half parkinsonism"), lack of benefit from levodopa, and imaging demonstrating evidence of cerebrovascular disease, either discrete strokes or confluent changes in the white matter often attributed to microvascular disease. What is labeled vascular parkinsonism is arguably overdiagnosed, and it is important to consider other causes such as a parkinsonian syndrome or normal pressure hydrocephalus.[16–18]

IMAGING OF THE PRESYNAPTIC DOPAMINE TRANSPORTER

Single-photon emission computed tomography imaging of the uptake of ioflupane I123 (DaTscan) by the presynaptic dopamine transporter is a marker of integrity of the dopaminergic nigrostriatal pathway and has a high sensitivity to detect its degeneration.[19–22] It was approved by the Food and Drug Administration in 2011 to distinguish tremor due to PD from essential tremor. It cannot distinguish between PD and other causes of parkinsonism also associated by nigrostriatal degeneration, which is virtually all of the parkinsonism syndrome (MSA, PSP, etc.) and in most cases the differential boils down to PD versus a related syndrome.

In the authors' view, DaTscan has a limited role in the evaluation of most patients with parkinsonism, particularly if one is familiar with and follows the MDS diagnostic criteria. Circumstances where it can be considered include the following: (1) if there is legitimate uncertainty about the cause of parkinsonism; if everything points toward PD, then imaging is not needed; (2) if the result will change management, and (3) if the diagnosis cannot be obtained in an easier and less expensive way and the first step here should be referral to a specialist in movement disorders.[23] Similarly, for many patients with an unclear cause of parkinsonism, the best test is often the "test of time" along with careful follow-up.

Nonmotor Features of Parkinson's Disease

As discussed earlier, the diagnosis of PD is based on its motor manifestations and these often get the most attention by physicians and patients. Yet, nonmotor symptoms (NMS) are present in all patients, are often as distressing as motor symptoms,

Downloaded for Anonymous User (n/a) at Duke University from ClinicalKey.com by Elsevier on February 07, 2022.
For personal use only. No other uses without permission. Copyright ©2022. Elsevier Inc. All rights reserved.

have a significant impact on quality of life, and are generally resistant to PD therapies directed at motor symptoms. Nonmotor symptoms cover a broad range of common PD symptoms and can be broadly classified into neuropsychiatric, sensory, sleep, and autonomic (**Box 3**).[24]

There are several reasons why being familiar with, inquiring about, and treating NMS is important. First, some NMS precede motor signs by years or decades (referred to as prodromal PD) and therefore could potentially be used to predict the onset of disease. These include reduced sense of smell, anxiety, depression, dream enactment (RBD), and constipation.[25] Second, the identification of these symptoms and their link to PD reduces patient and caregiver anxiety about the presence of another disorder. Third, these symptoms require therapies not usually tied to the treatment of motor symptoms

Box 3
Nonmotor features of PD

Neuropsychiatric
Mild cognitive impairment
Executive dysfunction
Dementia
Hallucinations
Delusions
Depression
Anxiety
Fatigue
Apathy
Autonomic
Constipation
Neurogenic bladder
Orthostatic hypotension
Erectile dysfunction
Diaphoresis
Drooling
Dysphagia
Sleep
REM behavioral disorder
Insomnia
Excessive daytime sleepiness
Restless legs syndrome and periodic limb movements of sleep
Sensory
Pain
Frozen shoulder
Hyposmia
Diplopia

Downloaded for Anonymous User (n/a) at Duke University from ClinicalKey.com by Elsevier on February 07, 2022.
For personal use only. No other uses without permission. Copyright ©2022. Elsevier Inc. All rights reserved.

and the presence of treatment-resistant neuroleptic malignant syndrome heralds increasing overall disability and reduced quality of life. In summary, recognizing and addressing the nonmotor features of PD are crucial to comprehensive care of those with PD.[26,27]

The nonmotor features of PD are reviewed in **Box 3**.

Treatment of Parkinson's Disease

Initiation of therapy

One of the first decisions in treating patients with PD is when to start medical therapy and with which agent. Before considering that, it should be noted that physical therapy intervention and exercise both are likely to be beneficial to patients, although the most useful form of each is uncertain.[28] In the authors' practice they recommend formal "Big and Loud" physical and speech therapies as well as exercise programs geared toward the PD population. Examples include dancing, boxing training, and Tai Chi. Initiating medical therapy is a personalized decision and usually is begun when the signs and symptoms of PD begin to significantly affect a patient's ability to perform their activities related to hobbies, recreational and social activities, and occupation. Less obvious factors such as embarrassment from a tremor, a reduced ability to exercise, and the presence of pain or anxiety should be considered as well.

The mainstay of PD treatment involves medications that deplete dopamine or mimic its effect at the dopamine receptor. The most effective medication is levodopa that is paired with carbidopa, a peripheral inhibitor of its breakdown to reduce side effects and maximize therapeutic efficacy. Alternatives to starting with levodopa include the use of dopamine agonists, monoamine oxidase B (MAO-B) inhibitors and in certain cases anticholinergics.

Medications Used to Treat Parkinson's Disease Motor Symptoms

Levodopa

Levodopa coupled with a DOPA decarboxylase inhibitor (carbidopa in the United States) is the most effective therapy for PD. Carbidopa does not readily pass through the blood-brain barrier, thereby allowing levodopa to be converted to active dopamine preferentially in the central nervous system, because dopamine also does not cross the blood-brain barrier. Initiation of therapy begins with a pill containing 25 mg of carbidopa and 100 mg of levodopa (25/100) titrated up to at least 3 times a day. It should all be given during the waking day (approximately 4–5 hours apart) because most patients do not need medication at night unless symptoms interfere with sleep. Using the 10/100 preparation does not provide adequate carbidopa to prevent the peripheral conversion of levodopa to dopamine and should not be used to initiate therapy. Because levodopa is associated with the onset of wearing off and dyskinesia, its use often had been delayed in favor of other treatments such as MAO-B inhibitors and dopamine agonists in early disease. This idea is now being challenged.[29] The current argument for using levodopa early is that other treatments often have more initial side effects and are less effective than levodopa and that the onset of motor complications is tied to disease duration and levodopa dose magnitude rather than duration of levodopa exposure.[29,30] This is not universally accepted, but initiating levodopa therapy early in the disease course is an acceptable option. Treatment of early PD with levodopa, however, should be limited to the lowest effective dose and some consideration should be given to "levodopa sparing" therapies such as dopamine agonists as the dose requirements of levodopa increase.

Other considerations with the initiation of levodopa therapy include side effects such as dizziness and gastrointestinal (GI) upset. Despite a reduction in

Downloaded for Anonymous User (n/a) at Duke University from ClinicalKey.com by Elsevier on February 07, 2022.
For personal use only. No other uses without permission. Copyright ©2022. Elsevier Inc. All rights reserved.

therapeutic efficacy, patients may dose with meals to reduce side effects. Protein intake reduces levodopa efficacy by competing with its transport ultimately into the brain, and patients should be aware of this when eating meals containing high-protein loads. Some patients will delay high-protein meals to the evening when optimal symptom control is not required or take extra medication around the time of a high-protein meal. In refractory patients, levodopa-induced nausea can be managed through the use of extra carbidopa, ondansetron, domperidone (not available In the United States), or trimethobenzamide, because more common antiemetics such as promethazine, metoclopramide, and prochlorperazine may worsen Parkinson's symptoms through their antidopaminergic effect.[31]

With advancing disease, levodopa dosing is increased in both dose strength and frequency. As these doses increase other side effects such as hallucinations, delusions, motor complications, and orthostatic hypotension become more common. As dosing increases there is at least the theoretic possibility that carbidopa may cross into the brain and limit levodopa effectiveness. Doses of 450 mg of carbidopa a day do not impair levodopa efficacy,[32] but higher doses should prompt consideration of using preparations such as 10/100 or 25/250 to limit the risk. In addition, the possibility of other side effects from higher dose carbidopa has been suggested, and some recommend reducing daily carbidopa dose to less than 200 to 300 mg/d in susceptible patients.[33]

An increase in the number of daily levodopa doses also increases the number of peaks and troughs in medication concentration and is more burdensome for the patient. In response to this, 2 approved longer-acting formulations of levodopa have been engineered. The controlled release formulation provides minimal extension of the levodopa effect, whereas extended release (C/L-ER, aka Rytary) seems to offer longer-lasting effect with less variation in levodopa concentration.[34,35] Carbidopa/levodopa extended-release capsules (Rytary) are available in 4 dose strengths, each containing 3 formulations of levodopa and carbidopa that generate peak plasma concentration at different times after ingestion. Therapy with this drug is hampered by high cost and difficulties in determining the optimal dose. Tables are available for conversion of standard therapies to C/L-ER; however, more than half of patients require higher doses.[36]

Dopamine agonists

Dopamine agonists mimic the effect of dopamine at the dopamine receptor. They have the benefit of less frequent dosing with pramipexole and ropinirole dosed 3 times a day or once a day if the long-acting preparation is used. Rotigotine comes in a patch formulation for continuous release transdermally. Their use early on delays the need for levodopa and thereby delays the onset of levodopa-induced dyskinesia.[35] Unfortunately, these medications do not offer the same degree of symptom relief as levodopa. In addition, side effects such as peripheral edema, orthostasis, impulse control disorders, skin irritation (seen with rotigotine), psychosis, sleepiness, and a troublesome withdrawal syndrome limit their utility, especially in older patients.[31] They can be used successfully for initial therapy in those patients especially fearful of dyskinesia, in those desiring less frequent medication dosing, and in those who are able to tolerate side effects. They have a role as add-on therapy to levodopa to reduce the length and severity of off time. Given their longer duration effect, dopamine agonists may be better at addressing overnight off time and morning akinesia, when oral dosing of levodopa is inconvenient. Adding a dopamine agonist to levodopa also serves as a levodopa-sparing agent,

Downloaded for Anonymous User (n/a) at Duke University from ClinicalKey.com by Elsevier on February 07, 2022.
For personal use only. No other uses without permission. Copyright ©2022. Elsevier Inc. All rights reserved.

reducing the need for higher or more frequent levodopa doses and therefore may reduce levodopa-induced side effects.[37] The use of dopamine agonist may worsen dyskinesia necessitating a reduction in levodopa dose or reduction/discontinuation of the dopamine agonist. Apomorphine, another dopamine agonist, is used as an acute rescue therapy for patients with wearing-off symptoms that are troublesome. It is administered as a subcutaneous injection with an onset of action between 7 and 20 minutes and a duration of action of about 90 minutes.[38] Initiation requires the use of trimethobenzamide to avoid nausea and a careful titration to find the optimal, tolerable dose.

Catechol-O-methyl transferase inhibitors

This class of medication inhibits the metabolism of both levodopa and dopamine, therefore prolonging the action of each.[39] In doing so, it also increases the likelihood of levodopa-induced side effects. For practical purposes, entacapone is the only member of this medication class in common use in the United States because tolcapone use is limited by the requirement of monitoring for liver toxicity. Patients should be advised about the propensity of entacapone to cause benign discoloration of urine. It may cause diarrhea, which is typically mild and self-limited and rarely severe, and this side effect can be delayed by weeks to several months after initiation. Entacapone is available in a combination pill along with carbidopa and levodopa. This is a more convenient option and has the added benefit of being available in multiple levodopa dose strengths. A third member of this class opicapone has been found to be clinically useful as a once-a-day medication but is not yet available in the United States.[28]

Monoamine oxidase B inhibitors

These medications impair the metabolism of dopamine and include selegiline, rasagiline, and safinamide. As a class they reduce wearing-off when added to L-DOPA and likely delay the initiation of levodopa when used as monotherapy.

Amantadine

Amantadine has a mild anti-parkinsonian effect but is more often used to reduce levodopa-induced dyskinesia (LID), although duration of the effect and appropriate dosing have been the subjects of debate.[40,41] Nonetheless, amantadine is often used chronically to treat LID usually dosed 2 or 3 times a day. Side effects include psychosis, edema, constipation, and livedo reticularis. More recently, ADS-5102 or Gocovri has been approved for LID. It is an extended release formulation of amantadine that is dosed at bedtime that seems to be more marginally more efficacious than the immediate release form in reducing “off” time and reducing dyskinesia.[42]

Trihexyphenidyl

Anticholinergic medications including trihexyphenidyl are most often used to treat PD tremor and their use is limited by side effects.[43] Older patients may be intolerant of this class due to memory impairment, confusion, and hallucinations. Other side effects include dry mouth, constipation, urinary retention, sedation, tachycardia, reduced perspiration, blurred vision, and GI upset. Despite these drawbacks, trihexyphenidyl can offer tremor relief in patients whose tremor is resistant to levodopa and who demonstrate an ability to tolerate the side effects. They can be used as monotherapy or with other agents, and may have a levodopa sparing effect, reducing the need for higher doses of levodopa that often are required to treat refractory tremor.

Downloaded for Anonymous User (n/a) at Duke University from ClinicalKey.com by Elsevier on February 07, 2022.
For personal use only. No other uses without permission. Copyright ©2022. Elsevier Inc. All rights reserved.

Interventional Therapies

Carbidopa/levodopa enteral suspension (Duopa)

Patients with advanced PD whose motor complications, including on-off fluctuation and dyskinesia, are refractory to standard therapies may benefit from a constant infusion of carbidopa and levodopa in the form of an enteral suspension. This therapy involves a surgically implanted jejunostomy connected to a pump that infuses medication directly into the proximal jejunum where levodopa absorption is maximal. Benefits of this therapy include a more constant delivery of drug that bypasses potentially problematic delayed gastric emptying. Patients typically receive a morning bolus dose of medication followed by a continuous maintenance dose. During the course of the day patients have the ability to self-administer extra doses to deal with off periods. The pump is typically disconnected at the end of the waking day. Studies have shown a reduction in daily off time by nearly 2 hours versus the use of standard levodopa oral formulation as well as a reduction in troublesome dyskinesia.[44,45] Drawbacks include surgical and device complications such as abdominal pain, infection, tube occlusion and dislocation, buried bumper syndrome, bezoars, leakage, and polyneuropathy. Also there is the inconvenience of jejunostomy maintenance, pump management, and carrying around the device all day. In selected patients, usually those with a dedicated caregiver to assist with device maintenance and who are reluctant to pursue or are poor candidates for DBS, significant benefit can be seen.

DEEP BRAIN STIMULATION

In a patient whose motor fluctuations are refractory and in those with poorly controlled disabling tremor, stimulation of deep structures of the brain offers significant relief. This therapy consists of placing thin wires containing distal electrodes stereotactically into the brain with the more proximal ends connected to extension cables that tunnel subcutaneously to an impulse generator (IPG). The IPG is placed beneath a patient's skin in the infraclavicular or intraabdominal region and stimulation parameters and location of stimulation among a series of distal contact sites are programmed using a remote device. Programming is done in the clinic and patients may adjust their device using a similar device within parameters set by the clinician programmer. DBS effectively reduces motor signs of the disease and improves off time, dyskinesia, and quality of life.[46] Before surgery, potential side effects of DBS including speech and cognition impairment, gait changes, and neuropsychiatric sequelae need to be considered as do surgical risks.[47] Careful selection of candidates for surgery involves psychiatric and cognitive screening, medical clearance, and involvement of experienced surgeons and device programmers. Patients with significant cognitive, medical, and psychiatric comorbidities are not ideal candidates. Management of expectations is important, and except for potentially better treatment of tremor and dyskinesia, patients should not expect benefit beyond their best preoperative symptom control on optimal medical therapy. Target selection among the 2 most common targets, the subthalamic nucleus and globus pallidus interna, considers the relative benefits of greater medication dose reduction and better tremor control seen in the former, with better dyskinesia control and potentially fewer side effects in the latter.[47] In patients with a tremor dominant presentation, targeting the ventral intermediate nucleus of the thalamus provides significant and sustained tremor relief and is considered in those whose overwhelming complaint is tremor.[48] In addition to site selection, other variables including the type of procedure (awake vs asleep), type of impulse generator (rechargeable or not, current steering or not), and brand of device (Medtronic, Abbott, or Boston Scientific each approved in

Downloaded for Anonymous User (n/a) at Duke University from ClinicalKey.com by Elsevier on February 07, 2022.
For personal use only. No other uses without permission. Copyright ©2022. Elsevier Inc. All rights reserved.

the United States) and whether to implant unilaterally or bilaterally are decisions made by an experienced clinical team.

REFERENCES

1. Parkinson J. An essay on the shaking palsy. London: Sherwood, Neely, and Jones; 1817. Available at: https://archive.org/details/essayonshakingpa00parkuoft.
2. Obeso JA, Stamelou M, Goetz CG, et al. Past, present, and future of Parkinson's disease: a special essay on the 200th Anniversary of the Shaking Palsy. Mov Disord 2017;32:1264–310.
3. Kalia LV, Lang AE. Parkinson disease in 2015: evolving basic, pathological and clinical concepts in PD. Nat Rev Neurol 2016;12:65–6.
4. Goedert M, Jakes R, Spillantini MG. The synucleinopathies: twenty years on. J Parkinsons Dis 2017;7:S51–69.
5. Deng H, Wang P, Jankovic J. The genetics of Parkinson disease. Ageing Res Rev 2018;42:72–85.
6. Postuma RB, Berg D, Stern M, et al. MDS clinical diagnostic criteria for Parkinson's disease. Mov Disord 2015;30:1591–601.
7. Köllensperger M, Geser F, Seppi K, et al. Red flags for multiple system atrophy. Mov Disord 2008;23:1093–9.
8. Boeve BF, Dickson DW, Duda JE, et al. Arguing against the proposed definition changes of PD. Mov Disord 2016;31:1619–22.
9. Rizzo G, Copetti M, Arcuti S, et al. Accuracy of clinical diagnosis of Parkinson disease: a systematic review and meta-analysis. Neurology 2016;86:566–76.
10. Gilman S, Wenning GK, Low PA, et al. Second consensus statement on the diagnosis of multiple system atrophy. Neurology 2008;71:670–6.
11. Quinn N. Multiple system atrophy-the nature of the beast. J Neurol Neurosurg Psychiatry 1989;(suppl):78–89.
12. McKeith IG, Boeve BF, Dickson DW, et al. Diagnosis and management of dementia with Lewy bodies: fourth consensus report of the DLB Consortium. Neurology 2017;89:88–100.
13. Höglinger GU, Respondek G, Stamelou M, et al, Movement Disorder Society-endorsed PSP Study Group. Clinical diagnosis of progressive supranuclear palsy: The movement disorder society criteria. Mov Disord 2017;32:853–64.
14. Williams DR, Lees AJ. Progressive supranuclear palsy: clinicopathological concepts and diagnostic challenges. Lancet Neurol 2009;8:270–9.
15. Armstrong MJ, Litvan I, Lang AE, et al. Criteria for the diagnosis of corticobasal degeneration. Neurology 2013;80:496–503.
16. Vizcarra JA, Lang AE, Sethi KD, et al. Vascular parkinsonism: deconstructing a syndrome. Mov Disord 2015;30:886–94.
17. Glass PG, Lees AJ, Bacellar A, et al. The clinical features of pathologically confirmed vascular parkinsonism. J Neurol Neurosurg Psychiatry 2012;83:1027–9.
18. Kalra S, Grosset DG, Benamer HT. Differentiating vascular parkinsonism from idiopathic Parkinson's disease: a systematic review. Mov Disord 2010;25:149–56.
19. Ba F, Martin WR. Dopamine transporter imaging as a diagnostic tool for parkinsonism and related disorders in clinical practice. Parkinsonism Relat Disord 2015;21:87–94.

Downloaded for Anonymous User (n/a) at Duke University from ClinicalKey.com by Elsevier on February 07, 2022.
For personal use only. No other uses without permission. Copyright ©2022. Elsevier Inc. All rights reserved.

20. Isaacson SH, Fisher S, Gupta F, et al. Clinical utility of DaTscan™ imaging in the evaluation of patients with parkinsonism: a US perspective. Expert Rev Neurother 2017;17:219–25.
21. Brooks DJ. Molecular imaging of dopamine transporters. Ageing Res Rev 2016; 30:114–21.
22. Rodriguez-Porcel F, Jamali S, Duker AP, et al. Dopamine transporter scanning in the evaluation of patients with suspected Parkinsonism: a case-based user's guide. Expert Rev Neurother 2016;16:23–9.
23. Zimmerman S. All my husband needed was a good physical examination. JAMA Intern Med 2015;175:340.
24. Barone P, Antonini A, Colosimo C, et al. The PRIAMO study: a multicenter assessment of nonmotor symptoms and their impact on quality of life in Parkinson's disease. Mov Disord 2009;24:1641–9.
25. Shrestha S, Kamel F, Umbach DM, et al. Nonmotor symptoms and Parkinson disease in United States farmers and spouses. PLoS One 2017;12:e0185510.
26. Titova N, Qamar MA, Chaudhuri KR. The nonmotor features of Parkinson's disease. Int Rev Neurobiol 2017;132:33–54.
27. Santos-Garcia D, de la Fuente-Fernandez R. Impact of non-motor symptoms on health-related and perceived quality of life in Parkinson's disease. J Neurol Sci 2013;332:136–40.
28. Fox SH, Katzenschlager R, Lim SY, et al. International Parkinson and movement disorder society evidence-based medicine review: update on treatments for the motor symptoms of Parkinson's disease. Mov Disord 2018;33(8):1248–66.
29. Matarazzo M, Perez-Soriano A, Stoessl AJ. Dyskinesias and levodopa therapy: why wait? J Neural Transm (Vienna) 2018;125:1119–30.
30. Cilia R, Akpalu A, Sarfo FS, et al. The modern pre-levodopa era of Parkinson's disease: insights into motor complications from sub-Saharan Africa. Brain 2014;137(Pt 10):2731–42.
31. Julius A, Longfellow K. Movement disorders: a brief guide in medication management. Med Clin North Am 2016;100:733–61.
32. Brod LS, Aldred JL, Nutt JG. Are high doses of carbidopa a concern? A randomized, clinical trial in Parkinson's disease. Mov Disord 2012;27:750–3.
33. Lau ACW, Diggle JL, Bring PP. Improvement in severe orthostatic hypotension following carbidopa dose eeduction. Can J Neurol Sci 2018;45:252–3.
34. Margolesky J, Singer C. Extended-release oral capsule of carbidopa-levodopa in Parkinson disease. Ther Adv Neurol Disord 2018;11. 1756285617737728.
35. Connolly BS, Lang AE. Pharmacological treatment of Parkinson disease: a review. JAMA 2014;311:1670–83.
36. Hauser RA, Hsu A, Kell S, et al. Extended-release carbidopa-levodopa (IPX066) compared with immediate-release carbidopa-levodopa in patients with Parkinson's disease and motor fluctuations: a phase 3 randomised, double-blind trial. Lancet Neurol 2013;12:346–56.
37. Talati R, Baker WL, Patel AA, et al. Adding a dopamine agonist to preexisting levodopa therapy vs. levodopa therapy alone in advanced Parkinson's disease: a meta analysis. Int J Clin Pract 2009;63:613–23.
38. Stacy M. Apomorphine: North American clinical experience. Neurology 2004; 62(6 Suppl 4):S18–21.
39. Nutt JG, Woodward WR, Beckner RM, et al. Effect of peripheral catechol-O-methyltransferase inhibition on the pharmacokinetics and pharmacodynamics of levodopa in parkinsonian patients. Neurology 1994;44:913–9.

Downloaded for Anonymous User (n/a) at Duke University from ClinicalKey.com by Elsevier on February 07, 2022.
For personal use only. No other uses without permission. Copyright ©2022. Elsevier Inc. All rights reserved.

40. Thomas A, Iacono D, Luciano AL, et al. Duration of amantadine benefit on dyskinesia of severe Parkinson's disease. J Neurol Neurosurg Psychiatry 2004;75:141–3.
41. Isaacson SH, Fahn S, Pahwa R, et al. Parkinson's Patients with dyskinesia switched from Immediate Release Amantadine to Open-label ADS-5102. Mov Disord Clin Pract 2018;5:183–90.
42. Paik J, Keam SJ. Amantadine extended-release (GOCOVRI™): a review in levodopa-Induced dyskinesia in Parkinson's disease. CNS Drugs 2018;32:797–806.
43. Olanow CW, Koller WC. An algorithm (decision tree) for the management of Parkinson's disease: treatment guidelines. American Academy of Neurology. Neurology 1998;50(3 Suppl 3):S1–57.
44. Olanow CW, Kieburtz K, Odin P, et al. Continuous intrajejunal infusion of levodopa-carbidopa intestinal gel for patients with advanced Parkinson's disease: a randomised, controlled, double-blind, double-dummy study. Lancet Neurol 2014;13:141–9.
45. Seeberger LC, Hauser RA. Carbidopa levodopa enteral suspension. Expert Opin Pharmacother 2015;16:2807–17.
46. Perestelo-Perez L, Rivero-Santana A, Perez-Ramos J, et al. Deep brain stimulation in Parkinson's disease: meta-analysis of randomized controlled trials. J Neurol 2014;261:2051–60.
47. Almeida L, Deeb W, Spears C, et al. Current practice and the future of deep brain stimulation therapy in Parkinson's disease. Semin Neurol 2017;37:205–14.
48. Cury RG, Fraix V, Castrioto A, et al. Thalamic deep brain stimulation for tremor in Parkinson disease, essential tremor, and dystonia. Neurology 2017;89:1416–23.

Downloaded for Anonymous User (n/a) at Duke University from ClinicalKey.com by Elsevier on February 07, 2022.
For personal use only. No other uses without permission. Copyright ©2022. Elsevier Inc. All rights reserved.