Chapter 10
Parkinson's Disease

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Clinical Pearls

- Parkinsonism is defined as bradykinesia plus the presence of either rigidity, tremor, or gait abnormality.
- PD is number 1 cause of parkinsonism, with asymmetric onset of symptoms that is slowly progressive and has an excellent levodopa response
- MSA can be considered when there is a presence of cerebellar signs along with parkinsonism without a significant levodopa response
- PSP can be considered with vertical gaze palsy, square wave jerks, and early onset of gait abnormality with falls.
- Drug-induced parkinsonism can occur in setting of any dopamine-depleting agent including typical antipsychotics, atypical antipsychotics, and anti-emetics.
- There are various options for treatment of PD that will depend on symptoms and age of patient; however, all patients should be encouraged to incorporate daily aerobic exercise.

Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disease after Alzheimer disease, affecting about 2% of the population over the age of 60. The prevalence of PD rises from 107/100,000 persons in age 50–59 years to 1087/100,000 persons in age 70–79 years [1]. Greater disease severity, and the

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presence of motor complications and cognitive issues have been correlated with higher costs and lower rates of employment [2–6]. Therefore, it is imperative to diagnose and optimally manage PD as early as possible.

Clinical Manifestation (History and Physical Examination)

Parkinsonism is defined by the presence of bradykinesia, in combination with either rest tremor, rigidity, or both. One of the main causes of parkinsonism is idiopathic PD.

Bradykinesia is best appreciated by investigating fine motor movements (e.g. finger tapping, hand grasps, wrist pronation and supination, toe tapping, and heel tapping), along with generalized body slowness (i.e. lack of spontaneous movement such as loss of facial expression ["masked facies"]), decreased weight shifting or leg crossing, slurred speech, and even hypophonia, due to improper movement of mouth and tongue. There may be bradyphrenia (slowness of thought), characteristically manifested by a delay in answering questions (even though the answer is correct). In the patient's history, bradyphrenia manifests as slowness in performance of daily activities and decreased reaction times [7–9].

Tremor is evaluated with the hand resting supine on the lap, with the elbow gently resting against the body (i.e., not braced by the arm of the chair). This allows the classic "pill-rolling" tremor in the hands to emerge, although other body parts such as the chin, lips, tongue, legs and feet can also shake. Often, a distracting maneuver may help elicit the resting tremor—for example, having the patient close his or her eyes while performing a mental task such as subtractions or reciting the months of the year in reverse order. Actively suspending the hand in the air does not test resting tremor but rather assesses the presence of postural tremor, which is more commonly noticed in essential tremor (ET). However, if the postural tremor appears after a delay of a few seconds, it is considered a "re-emergent tremor" that suggest a parkinsonian tremor, rather than the true postural tremor seen in ET [10]. Classically, for idiopathic PD, the tremor is more likely to start in a unilateral limb and progress bilaterally, although up to 20% of PD cases do not manifest with any tremor.

Rigidity is assessed with the limb at rest and the examiner passively (and slowly) flexing, extending and rotating the joint. Rigidity can be further described as "lead pipe" rigidity when the increase in tone is smooth, or "cogwheel" rigidity, when tremor is superimposed on the stiffness. Activating the contralateral limb (such as asking the patient to open and close the right hand while one examines the left arm) may enhance the rigidity [11]. Some patients have an intrinsic difficulty in relaxing, which can be mistaken for parkinsonian rigidity. Finally, "gegenhalten" or paratonia may be detected if the resistance seems to be conscious or variable with direction of assessment, which can be determined by suddenly letting go of the limb and noting that the patient was holding it up all along [12].

Gait abnormality in PD includes the sudden stopping of walking that may occur upon the appearance of an obstacle or a doorway (freezing of gait), the inability to turn easily (leading to the en bloc turn as well as difficulty pivoting when attempting to sit back in a chair) and difficulty in initiating a step (gait ignition failure). Other gait features that can be noted include dragging the foot of the more affected side, decreased swing of the arm on the affected side and history of falls. Posture tends to be flexed or hunched, and more advanced patients may skew to one side. Interestingly, if lower extremity symptoms predominate or if freezing of gait seems prominent, this may suggest a Parkinson plus syndrome or a vascular parkinsonism [13, 14].

The Unified Parkinson's Disease Rating Scale (UPDRS, especially the Movement Disorder Society modified version) is the gold standard scale used to assess motor severity, track disease progression, and response to treatment. It can also be utilized in clinics for the Parkinson-specific motor examination [15].

Along with describing these motor symptoms, PD patients have significant non-motor features that are frequently associated with the disorder. These symptoms, at times, tend to be very disabling and require thorough investigation [16, 17]. These features are outlined below:

- Hyposmia, or the loss of the sense of smell, frequently predates the onset of motor symptoms by possibly 5–10 years [18, 19].
- Sleep disturbances may include one or more of the following [20]:
  - The most common sleep disturbance in patients with PD is insomnia, affecting up to 88% of patients [21, 22].
  - Restless leg syndrome [23, 24]
  - REM behavior disorder ("acting out one's dreams" or purposeful actions during REM phase of sleep), which may predate the motor symptoms by years [25].
- Behavioral and cognitive symptoms including depression, anxiety, apathy, dementia, hallucinations, impulse control disorders all can be seen commonly in PD and require aggressive monitoring and treatment.
- Gastrointestinal symptoms include constipation, which occurs quite frequently, also often predating motor symptoms; gastroparesis; dysphagia (swallowing difficulties, which can predispose a patient to aspiration pneumonia); and sialorrhea (drooling)
- Urinary symptoms include urinary urgency and incontinence (resulting from bladder dyssynergia), along with nocturia
- Other autonomic symptoms include: erectile dysfunction, thermoregulatory dysfunction, and orthostatic hypotension (sense of lightheadedness when rising, can be seen as a result of PD as well as levodopa) [26, 27].
- Fatigue, which is often one of the most disabling non-motor symptoms of PD
- Seborrheic dermatitis

Diagnostic Approach

Upon evaluation in the clinic, if the above signs are present along with a history of having a sense of slowing down and other non-motor features, PD is high on the differential. Currently, there are no laboratory tests or imaging that can confirm the diagnosis of PD. Therefore, a thorough history and physical examination is key in diagnosing PD. The United Kingdom Parkinson's Disease Society Brain Bank Clinical Diagnostic Criteria (UKPDBBC) have been used as gold standard diagnostic tool in PD research (Table 10.1).

Table 10.1 Approach to diagnosis of Parkinson's disease

Step 1. Diagnosis of a Parkinsonian syndrome
• Bradykinesia and at least one of the following
– Muscular rigidity
– 4–6 Hz rest tremor
– Postural instability not caused by primary visual, vestibular, cerebellar, or proprioceptive dysfunction
Step 2. Exclusion criteria for Parkinson's disease (must answer 'no' to all these items)
• History of repeated strokes with stepwise progression of Parkinsonian features
• History of repeated head injury
• History of definite encephalitis
• Oculogyric crises
• Neuroleptic treatment at onset of symptoms
• More than one affected relative (although several familial PD syndromes have now been described, so this is now often removed from the list of exclusionary criteria)
• Sustained remission
• Strictly unilateral features after 3 years
• Supranuclear gaze palsy
• Cerebellar signs
• Early severe autonomic involvement
• Early severe dementia with disturbances of memory, language, and praxis
• Babinski sign
• Presence of cerebral tumor or communication hydrocephalus on imaging study
• Negative response to large doses of levodopa in absence of malabsorption
• MPTP exposure
Step 3. Supportive prospective positive criteria for Parkinson's disease (three or more required for diagnosis of definite Parkinson's disease along with Step 1)
• Unilateral onset
• Rest tremor present
• Progressive disorder
• Persistent asymmetry affecting side of onset most
• Excellent response (70–100%) to levodopa
• Severe levodopa-induced chorea
• Levodopa response for 5 years or more
• Clinical course of 10 years or more

Laboratory

There are no clinically available blood or cerebral spinal fluid tests for PD. Certain tests can be used to rule out mimickers, such as Wilson disease (which can manifest as a tremor, parkinsonian or dystonic syndrome) or thyroid abnormalities (hyperthyroidism can lead to tremors, hypothyroidism can present with slowness).

Imaging

Routine computerized tomography (CT) and magnetic resonance imaging (MRI) scanning are similarly unhelpful in diagnosing PD, except to rule out structural lesions. It is generally not necessary to obtain an imaging study if the clinical picture is clear.

Position emission tomography (PET) and single-photon emission computerized tomography (SPECT) scans can be useful in narrowing the diagnosis. A type of SPECT scan called a DaTscan™ (as the ligand binds to the dopamine transporter) distinguishes neuro-degenerative parkinsonian syndromes (which includes PD) from all other non-degenerative causes of parkinsonism (such as essential tremor, drug-induced parkinsonism and vascular parkinsonism) (Fig. 10.1) [28]. This scan, however, cannot distinguish PD from other "Parkinson-plus syndromes" such as multiple systems atrophy and progressive supranuclear palsy [17].

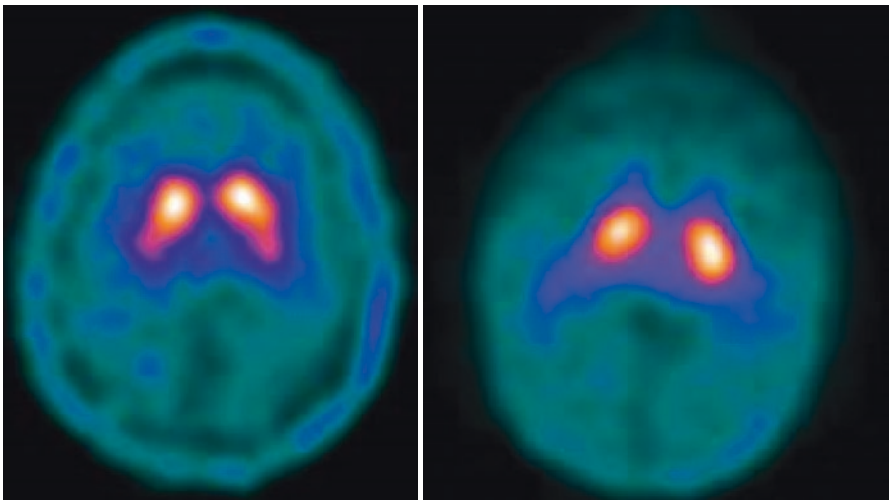

Fig. 10.1 DAT Scan with normal striatonigral activity (*left*) and abnormal activity characteristic of PD (*right*)

Ancillary Tests

Two ancillary diagnostic tests, olfactory loss and an abnormal metaiodobenzylguanidine (MIBG) scintigraphy (due to post-ganglionic sympathetic dysfunction in PD) have deemed reliable, with specificity >80% and may be used as a supportive criterion for diagnosis.

Diagnosis Criteria

Although the UKPDBBC criteria remains the research gold standard, the Movement Disorders Society has recently published the MDS Clinical Diagnostic Criteria for PD, incorporating both motor and nonmotor manifestations. The MDS-PD criteria incorporated many non-motor symptoms while retaining the central feature of parkinsonism (i.e. bradykinesia in combination with either rest tremor, rigidity or both). Similar to the UKPDBBC, after documentation of motor parkinsonism, the MDS-PD criteria proposed a list of absolute exclusions and red flags that argues against the diagnosis of PD, and supportive criteria that argue for PD diagnosis as the etiology of parkinsonism. Two levels of diagnostic certainty based on these positive and negative factors were proposed: clinically *established* PD and clinically *probable* PD [29] (Table 10.2).

Differential Diagnosis

For some of the non-motor features mentioned above, such as dementia, psychiatric features or orthostatic hypotension, if they are severe and out of proportion to the limb tremor and rigidity, a Parkinson-plus syndrome could be the diagnosis (such as multiple systems atrophy (MSA), progressive supranuclear palsy (PSP), corticobasal degeneration (CBD), or Lewy body disease (DLB)). In general, Parkinson-plus syndromes should also be considered when the patient has extreme sensitivity or equivocal response to levodopa. One elusive differential diagnosis is vascular parkinsonism, which can manifest with a shuffling gait but may not typically have the tremor and limb rigidity of idiopathic PD. Vascular parkinsonism is typically the result of chronic small vessel disease affecting the periventricular area, basal ganglia, or parts of the brainstem, resulting in walking problems. Drug-induced parkinsonism should be considered when a patient presents with symmetric parkinsonism along with a significant history of neuroleptic or antiemetic use. In general, drug-induced parkinsonism is characterized by less tremors and postural instability and more rigidity, but this is not an absolute rule. It is important to consider essential

Table 10.2 Diagnostic criteria for Parkinson's disease

The first essential criterion is parkinsonism, which is defined as bradykinesia, in combination with at least rest tremor or rigidity. Examination of all cardinal manifestations should be carried out as described in the MDS–UPDRS. See Fig. 10.2
Diagnosis of *Clinically Established PD* requires
• Absence of absolute exclusion criteria
• At least two supportive criteria
• No red flags
Diagnosis of *Clinically Probable PD* requires
• Absence of absolute exclusion criteria
• Presence of red flags counterbalanced by supportive criteria
– If one red flag is present, there must also be at least one supportive criterion
– If two red flags, at least two supportive criteria are needed
– No more than two red flags are allowed for this category
Supportive criteria
• Clear and dramatic beneficial response to dopaminergic therapy. During initial treatment, patient returned to normal or near-normal level of function. In the absence of clear documentation of initial response a dramatic response can be classified as
– Marked improvement with dose increases or marked worsening with dose decreases. Mild changes do not qualify. Document this either objectively (>30% in UPDRS III with change in treatment), or subjectively (clearly-documented history of marked changes from a reliable patient or caregiver)
– Unequivocal and marked on/off fluctuations, which must have at some point included predictable end-of-dose wearing off
• Presence of levodopa-induced dyskinesia
• Rest tremor of a limb, documented on clinical examination (in past, or on current examination)
• The presence of either olfactory loss or cardiac sympathetic denervation on MIBG scintigraphy
Absolute exclusion criteria: The presence of any of these features rules out PD
• Unequivocal cerebellar abnormalities, such as cerebellar gait, limb ataxia, or cerebellar oculomotor abnormalities (e.g., sustained gaze evoked nystagmus, macro square wave jerks, hypermetric saccades)
• Downward vertical supranuclear gaze palsy, or selective slowing of downward vertical saccades
• Diagnosis of probable behavioral variant frontotemporal dementia or primary progressive aphasia, defined according to consensus criteria within the first 5 years of disease
• Parkinsonian features restricted to the lower limbs for more than 3 years
• Treatment with a dopamine receptor blocker or a dopamine-depleting agent in a dose and time-course consistent with drug-induced parkinsonism
• Absence of observable response to high-dose levodopa despite at least moderate severity of disease
• Unequivocal cortical sensory loss (i.e., graphesthesia, stereognosis with intact primary sensory modalities, clear limb ideomotor apraxia, or progressive aphasia)

(continued)

Table 10.2 (continued)

• Normal functional neuroimaging of the presynaptic dopaminergic system
• Documentation of an alternative condition known to produce parkinsonism and plausibly connected to the patient's symptoms, or, the expert evaluating physician, based on the full diagnostic assessment feels that an alternative syndrome is more likely than PD
Red flags
• Rapid progression of gait impairment requiring regular use of wheelchair within 5 years of onset
• A complete absence of progression of motor symptoms or signs over five or more years unless stability is related to treatment
• Early bulbar dysfunction: severe dysphonia or dysarthria (speech unintelligible most of the time) or severe dysphagia (requiring soft food, nasogastric tube, or gastrostomy feeding) within first 5 years
• Inspiratory respiratory dysfunction: either diurnal or nocturnal inspiratory stridor or frequent inspiratory sighs
• Severe autonomic failure in the first 5 years of disease. This can include
– Orthostatic hypotension—orthostatic decrease of blood pressure within 3 min of standing by at least 30 mmHg systolic or 15 mmHg diastolic, in the absence of dehydration, medication, or other diseases that could plausibly explain autonomic dysfunction, or
– Severe urinary retention or urinary incontinence in the first 5 years of disease (excluding long-standing or small amount stress incontinence in women) that is not simply functional incontinence. In men, urinary retention must not be attributable to prostate disease, and must be associated with erectile dysfunction
• Recurrent (>1/year) falls because of impaired balance within 3 years of onset
• Disproportionate anterocollis (dystonic) or contractures of hand or feet within the first 10 years
• Absence of any of the common nonmotor features of disease despite 5 years disease duration. These include sleep dysfunction (sleep-maintenance insomnia, excessive daytime somnolence, symptoms of REM sleep behavior disorder), autonomic dysfunction (constipation, daytime urinary urgency, symptomatic orthostasis), hyposmia, or psychiatric dysfunction (depression, anxiety, or hallucinations)
• Otherwise-unexplained pyramidal tract signs, defined as pyramidal weakness or clear pathologic hyperreflexia (excluding mild reflex asymmetry and isolated extensor plantar response)
• Bilateral symmetric parkinsonism. The patient or caregiver reports bilateral symptom onset with no side predominance, and no side predominance is observed on objective examination

tremor (ET) when the patient has action tremors without rigidity and subsides with alcohol. Since ET also commonly afflicts the elderly, it is not uncommon for these patients to have some degree of bradykinesia. Enhanced physiologic tremors can be occur when the sympathetic nervous system is "over-stimulated" such as in hyperthyroidism, anxiety, and use of anti-asthma inhalers and steroids. Depression can be associated with slowness of movement (termed psychomotor retardation) but typically without tremors at rest or rigidity, and depressed mood is the main complaint.

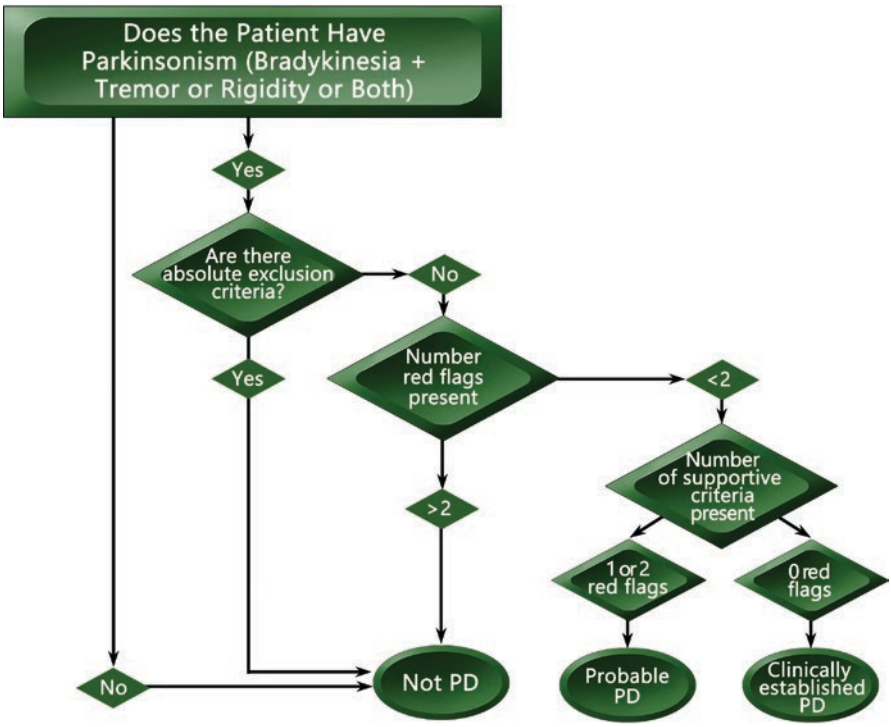

Fig. 10.2 Approach to diagnosis of Parkinson's disease

Therapeutics

Initiating treatment and choosing a drug are very individualized decisions. Age, disease severity, insurance and financial state, work status, and even the predominantly affected side can play a role in the timing of initiation and in pharmacological selection. The following discussion is to be used as a guideline that can be modified based on influencing circumstances. Figure 10.3 describes the suggested treatment approach. While general therapeutic principles should be practiced, it is critical to individualize therapy to the patient. Older patients are more predisposed to developing side effects from adjunctive PD medications, and less likely to develop levodopa-induced dyskinesias. Therefore, they are generally best initiated on levodopa, regardless of disease severity [30].

Table 10.3 summarizes an approach to selecting the initial therapy for a newly diagnosed patient with PD.

Levodopa is still the most efficacious anti-parkinsonian agent available [31]. There are multiple formulations of levodopa including immediate-release carbidopa/levodopa (Sinemet), carbidopa/levodopa controlled release (Sinemet CR), carbidopa/levodopa/entacapone (Stalevo), dissolvable carbidopa/levodopa (Parcopa)

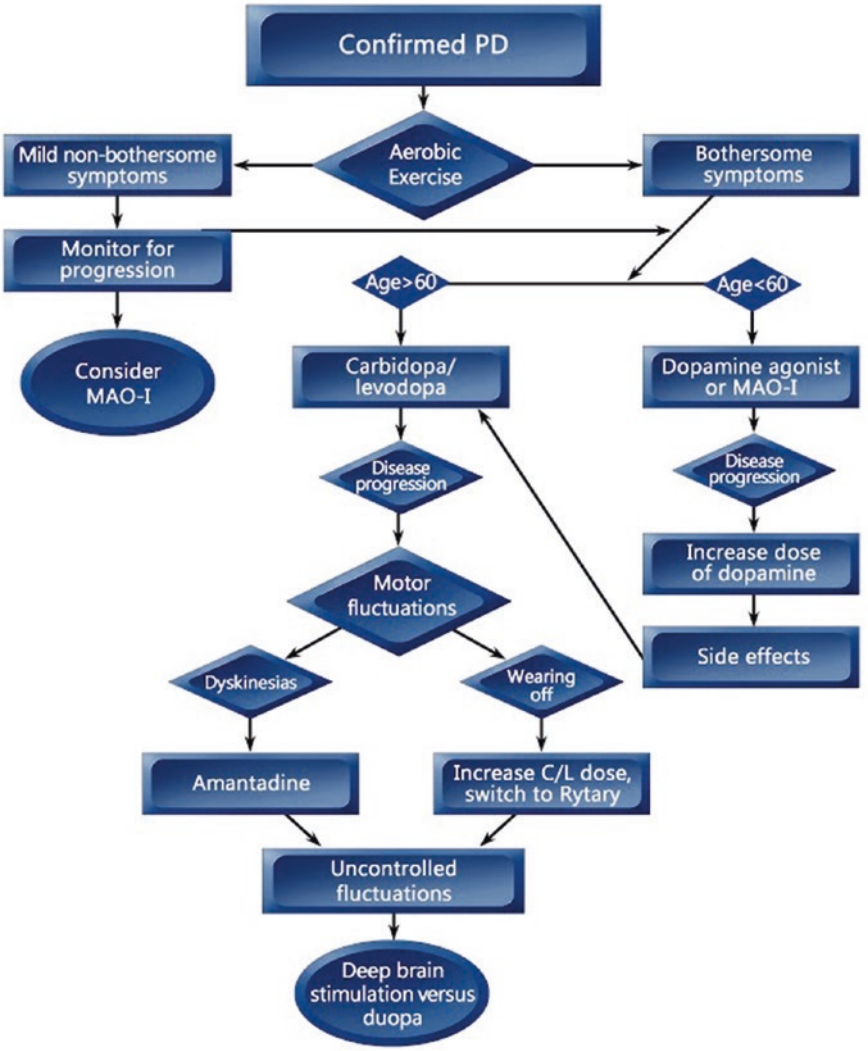

Fig. 10.3 Approach to management of Parkinson's disease

and most recently, carbidopa/levodopa extended release (Rytary). These medications are generally started three times a day (during awake hours to get most symptomatic benefit) and initially with meals (to minimize nausea and vomiting). Rytary is the latest formulation of levodopa in capsule form (containing short-, medium- and long-acting levodopa) designed to extend benefit in patients who may be wearing off prior to their next dose.

The most recognized long-term risks of levodopa use are motor fluctuations and dyskinesias. They can occur in any PD patient, but these are more likely to be

Table 10.3 How to select an initial antiparkinsonian agent

Situation	Consider using this drug/class	Side effects/issues to consider or be aware of
Tremor predominant		
– Older patient – Younger patient	– Dopamine agonist or levodopa – AC, amantadine, DA, LD	DA side effects: sleep attacks in working patients and cognitive issues in the elderly
Young onset		
– Mild – Severe	– Amantadine, MAOI, DA – Levodopa	DA side effects: sleep attacks, compulsive behaviors and leg edema after long-term use
Older onset (regardless of severity)	Levodopa	
Associated with depression	Dopamine agonist	DA side effects
History of compulsive behavior	Levodopa	Be aware of worsening psychosis
Gait and postural predominance, falls, instability	Levodopa	

Medications listed by abbreviation: *AC* anticholinergics, *DA* dopamine agonists, *LD* levodopa, *MAOI* MAO-B inhibitors

experienced by younger-onset patients. While dyskinesias are more likely to occur with levodopa use than with dopamine agonists (discussed below), for many patients, particularly older ones, the side effect profile of levodopa is more favorable than that of an agonist. It is also useful to keep in mind that most dyskinetic activity, when they do occur, are generally non-bothersome or treatable.

Commonly used dopamine agonists include pramipexole and ropinirole (in a standard or extended-release formulation), rotigotine (in a patch) and apomorphine (injectable). Pramipexole, ropinirole and rotigotine can be used as initial monotherapy or as an adjunctive treatment to levodopa in the presence of wearing off or motor fluctuations. Apomorphine is used as a rescue agent when wearing-off is occurring, and when most other therapies have failed. As a class, dopamine agonists are less likely to cause dyskinesias and may be more effective for the control of tremors [32]. However, compared to levodopa, they have a higher likelihood of causing dopaminergic side effects such as light-headedness, sedation, confusion and hallucinations. In addition, idiosyncratic drug class adverse effects include leg swelling (which may not be responsive to diuretics), "sleep attacks", as well as compulsive behaviors such as compulsive spending, pathological gambling, binge eating, punding, and hypersexuality.

Younger patients may similarly respond to amantadine, a drug of unclear mechanism of action, although purportedly acts as an NMDA-antagonist. This medication has a side effect profile includes hallucinations, insomnia, nausea, leg

swelling and 1% of the population may experience a purple lace-like appearing rash termed livido reticularis and so should be used with caution in older patients for PD symptom control. However, this medicine has multiple effects, including working to minimize levodopa-induced dyskinesias, and so for this latter purpose, it may be judiciously prescribed for patients of all ages [33].

Anticholinergic agents such as trihexyphenidyl and benztropine have been frequently used as levodopa-sparing options. Unfortunately, they have the side effects of confusion and hallucinations. In addition, perhaps they work only on tremor and less well on rigidity, though that may be debated.

The monoamine oxidase B inhibitors selegiline and rasagiline have been thought to possibly have a "neuroprotective benefit" although this belief continues to be debated to this day [34, 35]. They are generally well-tolerated, and are perceived to have a milder efficacy, and are therefore commonly used as initial monotherapy for PD. Rasagiline is also indicated as an add-on therapy to levodopa for motor fluctuations with relatively equal efficacy to COMT inhibitors [36, 37]. Because of the selective nature of its MAO inhibition, fears of drug-drug interaction and tyramine reactions, when using selegiline and rasagiline at recommended doses, are largely theoretical than a true practical concern.

Equally important, maintaining an active aerobic exercise regimen can be very beneficial in PD [38–40]. Options include stationary bike, treadmill, elliptical, yoga, tai chi, etc.

Figure 10.3 presents a suggested algorithm when treating a PD patient. When patients have symptoms that are bothersome enough to warrant treatment, age is an important factor to consider when deciding a medication. Older patients are at higher risk of side effects from dopamine agonists, and therefore carbidopa/levodopa is an appropriate first option. As the disease progresses, patients can experience motor fluctuations, as mentioned above. Older patients have a higher risk of cognitive impairment from PD medications. Therefore, in the presence of confusion, encephalopathy, delusions or bothersome hallucinations, it is imperative to simplify PD regimen by "peeling off" agents in this order:

1. Anticholinergic agents
2. Amantadine
3. MAO inhibitors
4. Dopamine agonists
5. COMT inhibitors
6. Levodopa

In PD patients with dementia, psychosis or sensitivity to medications, simply placing the on levodopa monotherapy may provide the greatest benefit-risk ratio.

Advanced treatment options including deep brain stimulation (DBS) and/or continuous levodopa infusion (Duopa) are considered when patients continue to experience motor fluctuations despite optimal use of conventional pharmacological treatment options. Duopa is a carbidopa/levodopa enteral suspension delivered through a PEG-J tube via an external pump, providing a stable level of levodopa, thereby alleviating motor fluctuations.

DBS was approved as a surgical treatment for PD by the Food and Drug Administration (FDA) in 2002 and currently is standard of care for advanced PD patients with significant motor complications, and for patients with treatment-refractory debilitating tremors. However, due to recent reports suggesting better quality of life among PD patients experiencing motor fluctuations for only 2 years, when receiving DBS as compared to best medical therapy, new guidelines have made DBS available for PD patients earlier in their disease course:

1. Diagnosis of PD for at least 4 years' duration with levodopa-responsive symptoms that are not adequately controlled with medication.
2. Motor complications from 4 months to 3 years
3. Motor complications of longer-standing duration.

Major advantages of DBS include its reversibility, and its ability to be modulated over time with disease progression or the occurrence of side effects or new symptoms. However, there is risk for infection, intracranial bleeding, and a patient should ideally be within close distance to a DBS center. DBS is contraindicated in patients with cognitive dysfunction. It is most ideal to have a multidisciplinary team when evaluating a patient for DBS with assessments from neurosurgery, neurology, neuropsychology and psychiatry (if needed). Patients and their families should have realistic expectations, including the recognition that DBS is not a cure and, generally speaking, with the exception of tremors and dyskinesias, the expectation that only PD symptoms that are responsive to their levodopa will respond to surgery.

ICD10 code

- Diseases of the nervous system G00-G99
  - Extrapyramidal and movement disorders G20-G26

    Parkinson's disease G20-

    Hemiparkinsonism
    Paralysis agitans
    Parkinsonism or Parkinson's disease NOS
    Primary Parkinsonism or Parkinson's disease

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Additional information can be found in

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