Parkinson Disease

1-Parkinson disease (PD) is a chronic, **progressive movement disorder** resulting from **loss of dopamine** from the nigrostriatal tracts in the brain, and is characterized by **rigidity**, **bradykinesia**, **postural disturbances**, and **tremor** [(1)].

2-The age at onset of PD is variable, usually ***between 50 and 80 years***, with a **mean onset of 55** years [(1)].

3-The **symptoms of PD are progressive**, and within 10 to 20 years, significant immobility results for most patients [(1)].

Etiology

The etiology of PD is poorly understood. Most evidence suggests it is **multifactorial**, and attributable to a complex interplay between **age-related changes** in brain, underlying **genetic** risks, and **environmental** triggers [(1)].

Pathophysiology

1-Parkinson's disease is a **degenerative process involving the dopaminergic neurons** in the **substantia nigra** (the area of the basal ganglia that produces and stores the neurotransmitter dopamine). This area plays an important role in the extrapyramidal system, which controls posture and coordination of voluntary motor movements [(2)].

2-**The loss of dopamine-producing neurons in the substantia nigra results in an imbalance between dopamine, an inhibitory neurotransmitter, and the excitatory neurotransmitter acetylcholine** [(3)]. This leads to an excess of excitatory acetylcholine at the synapse, and consequent rigidity, tremors, and bradykinesia [(2)].

3-Other **nondopaminergic** neurons may be affected, possibly contributing to **depression** and the other **non-motor symptoms** associated with this disease [(2)].

Clinical Presentation of Parkinson's disease

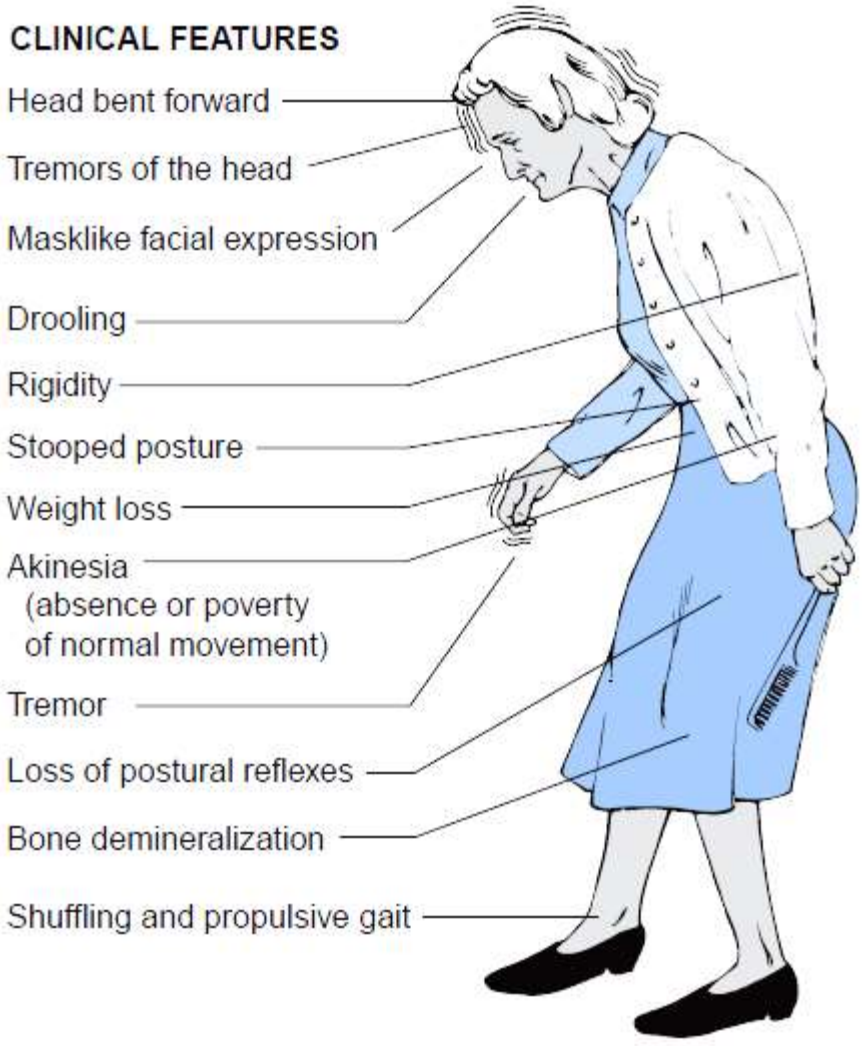
PD develops insidiously and progresses slowly [(4)]. Patients with PD display both ***motor and non-motor*** symptoms. The non-motor symptoms may precede the motor symptoms [(5)]. Clinical features are summarized in Table 1[(5)] and figure 1 [(1)].

Table 1: Clinical Presentation of PD	
Motor Symptoms (**TRAP**)	Non-motor Symptoms (**SOAP**)
T = ***T***remor at rest ("pill rolling") ***R*** = ***R***igidity (stiffness and cogwheel rigidity) ***A*** = ***A***kinesia or bradykinesia ***P*** = ***P***ostural instability and gate abnormalities	***S*** = ***S***leep disturbances (insomnia, restless legs syndrome(RLS)) ***.*** ***O*** = ***O***ther miscellaneous symptoms (problems with nausea, fatigue, speech, pain, dysesthesias, vision, seborrhea) ***A*** = ***A***utonomic symptoms (drooling, constipation, sexual dysfunction, urinary problems, sweating, orthostatic hypotension, dysphagia) ***P*** = ***P***sychological symptoms (anxiety, psychosis, cognitive impairment, depression)
Restless legs syndrome (RLS), is characterized by one or more of the following: urge to move the legs, **Relief of symptoms with movement , Onset or exacerbation of symptoms at rest** , Onset or worsening **of symptoms during nighttime** [(1)]**.**	

1-Tremor motion in the hands is often described as "**pill rolling**," since the fingers and thumbs move in opposition as though a small object was being rolled between them [(6)].

2-Bradykinesia **i**s a slowing of movement [(6)]. Slowness of movement characterized by *a slow, shuffling gait and lack of arm swing* [(7)].Movement becomes increasingly impaired and can make turning in bed, rising from a low chair, and even walking increasingly difficult [(6)].

3-Postural instability is the primary cause of falls associated with PD.
Signs include *flexion* at the *knees*, *hips*, and *waist* and *walking on the balls of the feet* [(6)].



4-Rigidity is an increase of muscle tone that is elicited when the examiner moves the patient's limbs, neck, or trunk [(8)]. Rigidity of the face and trunk is often observable as a lack of facial expression (***masked facies***). The masking of facial expression may be misinterpreted as apathy, or depression [(7)].

Diagnosis

1-The diagnosis is ***made clinically***, as there ***is no diagnostic test*** for Parkinson's disease [9].

2-Definite PD is diagnosed when there ***is at least two of the following***: resting **tremor**, **rigidity**, **bradykinesia**, and a **positive response to antiparkinson** medication [4].

3-Other diagnostic tests:

A-Neuroimaging may be useful for excluding other causes of PD.

B-Medication history: should be obtained to rule out drug-induced Parkinsonism [4].

Treatment

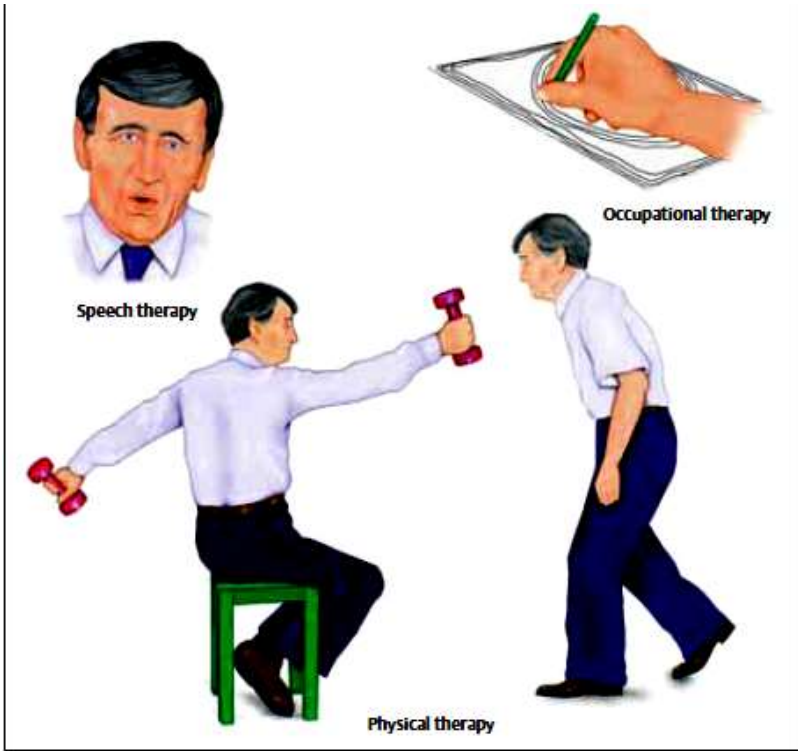
1-No cure is known for PD; therefore, treatment is symptomatic only [3].

2-The treatment of PD is categorized into **3 phases**:

A-**Lifestyle changes, nutrition, and exercise** [5].

B-**Pharmacologic intervention**, primarily with drugs that enhance dopamine concentrations [5].

C-**Surgical treatments** [5].



3-The current approach to treatment is to **delay medication therapy until the symptoms begin to interfere with the patient's ability to function or impact their quality of life (QOL)** [5].

Nonpharmacologic Therapy

1-Exercise, **physiotherapy**, and good **nutritional support** can be beneficial at the earlier stages to improve mobility, and enhance well-being and mood [1].

2-Speech therapy may be helpful, and **psychological support** is often necessary in dealing with depression and other related problems [1].

Drug therapy

The primary objective of drug therapy is to ***enhance dopaminergic activity*** within the damaged areas of the basal ganglia, and this is achieved in various ways (Table 6.26) [10].

Table 6.26 Pharmacological rationales for enhancing dopaminergic transmission in the basal ganglia

Approach	Rationale	Drug group and examples
Reduce cholinergic activity	Balance diminished dopaminergic activity	Antimuscarinic, e.g. trihexyphenidyl (benzhexol), procyclidine
Inhibit neuronal dopamine re-uptake	Maximize remaining dopaminergic activity	Amantadine
Stimulate dopamine receptors	Mimic dopamine	Dopamine agonist: • Ergot derived: cabergoline, pergolide, lisuride, bromocriptine • Non-ergot derived: ropinirole, rotigotine, pramipexole • Other: apomorphine
Supply dopamine precursor	Increase dopamine level in basal ganglia	Levodopa
Reduce peripheral destruction of precursor	Increase levodopa penetration into brain	Decarboxylase inhibitor, e.g. carbidopa, benserazide COMT-inhibitor: entacapone, tolcapone
Reduce central destruction of dopamine	Increase dopamine half-life in brain	COMT-inhibitor: tolcapone MAO-B inhibitor, e.g. selegiline. rasagiline

MAO-B, monoamine oxidase-B; COMT, catechol-O-methyl transferase.

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A-Levodopa and Carbidopa/Levodopa

1- L-dopa, ***the most effective drug available***, is the immediate precursor of dopamine. Ultimately, all PD patients will require L-dopa [(4)].

2- The decision whether to start L-dopa as soon as the diagnosis is made or only when symptoms compromise QOL has generated **controversy** [(4)].

3- ***Carbidopa*** or ***benserazide*** , which does not cross the blood– brain barrier, inhibit the peripheral conversion of L-dopa to dopamine. They therefore increase the CNS penetration of L-dopa and decreases adverse effects from peripheral L-dopa metabolism to dopamine [(4)].

4- The immediate response to levodopa is often dramatic, **but the long-term use is limited by the development of motor fluctuations**. The most common of these is the **wearing-off effect** [(11)].

1-Wearing off effect

The terms "off" and "on" refer to periods of poor movement (i.e., return of tremor, rigidity, or slowness) and good movement, respectively.

Wearing off occurs when patients experience recurrence of symptoms before the next dose of medication [(6)].

Possible options to solve such problem include [(4)]:

A-Carbidopa/L-dopa needs to be given ***more frequently*** so as to minimize daytime off episodes and to maximize on time [(4)].

B- ***The addition of the COMT inhibitor entacapone or the MAO-B inhibitor rasagiline*** extends the action of L-dopa, and either should be considered [(4)].

C- A ***dopamine agonist (e.g., pramipexole***, ***ropinirole***) also can be added to a carbidopa/L-dopa regimen in an attempt to minimize the occurrence of wearing off. For acute off episodes, a s***ubcutaneously administered short-acting dopamine agonist, apomorphine, i***s available and possesses a rapid onset of effect (within 20 minutes). It is administered as needed [(4)].

Another complication of L-dopa therapy is **dyskinesia**

2-Dyskinesias.:

Dyskinesia **is an involuntary choreiform movements (**too much movement)**involving the neck, trunk, and lower/upper extremities.** Dyskinesia usually is associated with **peak dopamine** levels (peak-dose dyskinesia) [(4)].

Possible options to solve such problem include [(4)]:

A-The **use of lower individual doses of L-dopa (**with an increase in dosage frequency or addition of another agent to counteract the effects of using a lower L-dopa dose) [(4)].
B-Addition of amantadine [(4)].

B-Dopamine Agonists

1- The ergot derivative ***bromocriptine*** and the nonergots ***pramipexole*** , ***rotigotine*** , and ***ropinirole*** are beneficial adjuncts in patients with limited clinical response to L-dopa. ***They decrease the frequency of "off" periods and provide an L-dopa-sparing effect*** [(4)]..

2-The **nonergots are safer and are effective as monotherapy** in mild-moderate PD as well as adjuncts to L-dopa [(4)].

3-**Note: important**: Guidelines from the American Academy of Neurology support either dopamine agonists or levodopa as initial therapy for PD [(4)].

A-**In younger patients (e.g., age <65 years)** with milder disease, the initiation of a **dopamine agonist is preferred** [(1)].

B- **In older patients (e.g.,age >65 years)** with PD, it may be more appropriate to **initiate treatment with levodopa** instead of a dopamine agonist [(1)].

The reason for this recommendations are:

1-There is less risk of developing motor complications from dopamine agonists than from L-dopa. **Because younger patients are more likely to develop motor fluctuations, dopamine agonists are preferred in this population** [4].

2-Older patients are more likely to experience psychosis from dopamine agonists; therefore, carbidopa/L-dopa may be the best initial medication in elderly patients [4].

C-Catechol-O-Methyltransferase (COMT) Inhibitors

1-Tolcapone and entacapone are ***used only in conjunction with carbidopa/L-dopa to prevent the peripheral conversion of L-dopa to dopamine.*** Thus, "on" time is increased by about ~1 to 2 hours. These agents significantly decrease "off " time and decrease L-dopa requirements.

2- Tolcapone can cause ***hepatotoxicity***. ***There is no evidence of hepatotoxicity from entacapone*** [4].

D-Monoamine Oxidase Type-B (MAO-B) Inhibitors

1-Inhibition of MAO-B is associated with reduced synaptic degradation of dopamine and prolonged dopaminergic activity. Two selective MAOB inhibitors, rasagiline and selegiline, are available for management of PD [7].

2-**Selegiline is a first-generation MAO-B inhibitor** [7] that blocks dopamine breakdown and can *modestly extend the duration of action of L-dopa (up to 1 hour)* [4]. Selegiline is metabolized to the **amphetamine derivative**s , which have been implicated in producing side effects such as **insomnia** and vivid dreaming [7].

A-It is **not given in the evening** because excess stimulation from metabolites can cause insomnia [1].

B-The **orally disintegrating tablet** formulation dissolves in the mouth on contact with saliva and undergoes pregastric absorption. This is an improvement over conventional selegiline because it minimizes the effect of first-pass metabolism and results in higher plasma concentrations of selegiline and **reductions in the amphetamine-based metabolites** [1].

3-**Rasagiline** is a second-generation selective inhibitor of MAO-B. It is indicated as monotherapy in early disease or as adjunct therapy to levodopa in advanced disease [1].

A-Rasagiline is differentiated from selegiline primarily in that it is a more **potent inhibitor of MAO-B, and it is not metabolized into amphetamine**-based metabolites [1].

B-When an adjunctive agent is required for managing motor fluctuations, rasagiline may provide 1 hour of extra "on" time during the day. It is considered a first-line agent (as is entacapone) for **managing motor fluctuations** [4].

E-Anticholinergic Medications

1-Anticholinergics (e.g. **procyclidine, and trihexyphenidyl (benzhexol))** are more helpful in alleviating **tremor and rigidity** than bradykinesia [12] (rarely show substantial benefit for bradykinesia) [4]. However, they are **poorly tolerated** by elderly patients owing to their cognitive side effects [12].

2-Their use is mostly **restricted to patients with tremor that is intractable to levodopa treatment** [11].

F-Amantadine

1-For patients with **mild signs and symptom**s, amantadine monotherapy may be considered [7]. **Amantadine reduces all the symptoms of parkinsonian**, usually within days after starting therapy; however, long-term use is limited in many patients by the development of **tachyphylaxis** within 1 to 3 months [1].

2-Aamantadine has been found to **have antidyskinesia effects,** the finding has shifted its emphasis from use as monotherapy in early disease to that of an **adjunctive agent in managing levodopa-induced dyskinesias** [1, 7].

(Because excess glutamatergic activity has been implicated in the pathophysiology of dopaminergic dyskinesias [1] and amantadine has glutamate-antagonist properties) [11].

General approach to treat Parkinson disease [4].

1-Monotherapy usually begins with a monoamine oxidase-B (MAO-B) inhibitor, or if the patient is physiologically young, a dopamine agonist.

2-For patients who are older, cognitively impaired, or having moderately severe functional impairment, L-dopa (e.g., carbidopa/levodopa) is preferred.

3- With the development of motor fluctuations:

A- addition of a COMT inhibitor should be considered to extend L-dopa duration of activity.
B-Alternatively, addition of a MAO-B inhibitor or dopamine agonist should be considered.
C- For management of L-dopa-induced peak-dose dyskinesias, the addition of amantadine should be considered.

Surgery

1-**Deep brain stimulation** involves the **implantation** of **a high-frequency device that provides electrical stimulation of the specific areas in the brain** [1].

2-Deep brain stimulation is reserved for patients **who have a good response to levodopa but in whom dyskinesias or response fluctuations are problematic** [12].

Management of Common Nonmotor Symptoms of Parkinson's Disease

Pharmacologic and nonpharmacologic treatment interventions for nonmotor symptoms of Parkinson's disease are summarized by the following tables (table 2, 3 and 4) [13].

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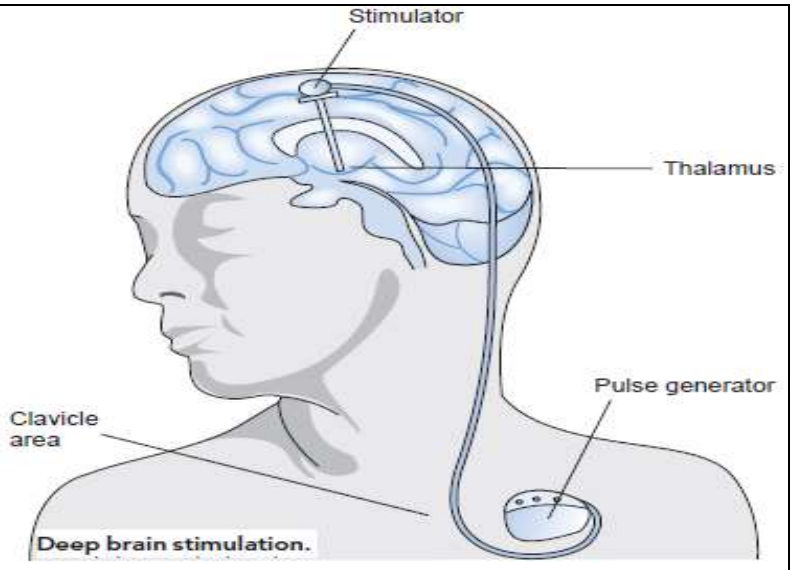

Deep brain stimulation. A pulse generator, sends high-frequency electrical impulses to the thalamus, thereby blocking the nerve pathways associated with tremors in Parkinson disease [1].

Table 2. Select Interventions and Medications for the Management of Cognitive Impairment and Psychosis in PD

Cognitive Impairment
Assess anticholinergic burden
Medications (initial dosing)
Donepezil 5 mg/day
Galantamine 4 mg twice daily (immediate release) or 8 mg/day (extended release)
Rivastigmine 1.5 mg twice daily (oral) or 4.6 mg/day (patch)
Psychosis
Discontinue or reduce dosages of medications in the following order: anticholinergics, MAO-B inhibitors, amantadine, dopamine agonists, COMT inhibitors, levodopa
Medications
Clozapine 6.25 mg/day, titrated to effect
Quetiapine 12.5 mg/day, titrated to effect

COMT: catechol O-methyltransferase; MAO-B: monoamine oxidase B; PD: Parkinson's disease.
Source: References 17, 25, 31, 32.

Table 3: Select Interventions and Medications for the Management of Dysphagia, Sialorrhea, and Gastrointestinal Dysfunction in PD

Dysphagia
Eat in an upright position and tuck chin to neck
Eat smaller bites at a slower rate, followed by a cough
Use a thickening product for thin liquids
Sialorrhea
Evaluate medications for contributors
Botulinum toxin A
Atropine ophthalmic drops, used sublingually
Gastrointestinal Dysfunction
Assess anticholinergic burden
Encourage fluid/fiber intake
Physical activity
Medications (for constipation)
Psyllium
Methylcellulose
Docusate
Magnesium hydroxide
Lactulose
Polyethylene glycol
Senna
Medications (for gastroparesis)
Domperidone (not FDA approved in United States)
Avoid centrally acting dopamine blockers (e.g., metoclopramide)

PD: Parkinson's disease.
Source: References 2, 45-47, 49, 50.

Prognosis

1-The outlook for patients with Parkinson's disease is variable, **and depends partly on the age of onset** [9].

2-**If symptoms start in middle life**, the disease is usually slowly **progressive and likely to shorten lifespan** because of the complications of immobility and tendency to fall [9].

3-**Onset after 70 is unlikely to shorten life** or become severe [9].

Table 4. Select Interventions and Medications for the Management of Orthostatic Hypotension in PD

Wear elastic stockings
Increase salt intake
Increase caffeine use
Avoid high temperatures, alcohol, and sudden postural changes
Examine medication regimen for possible contributors
Medications
Fludrocortisone 0.1-0.3 mg/day
Midodrine 2.5-10 mg/day
Indomethacin titrated to effect

PD: Parkinson's disease.
Source: References 3, 25, 53.

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