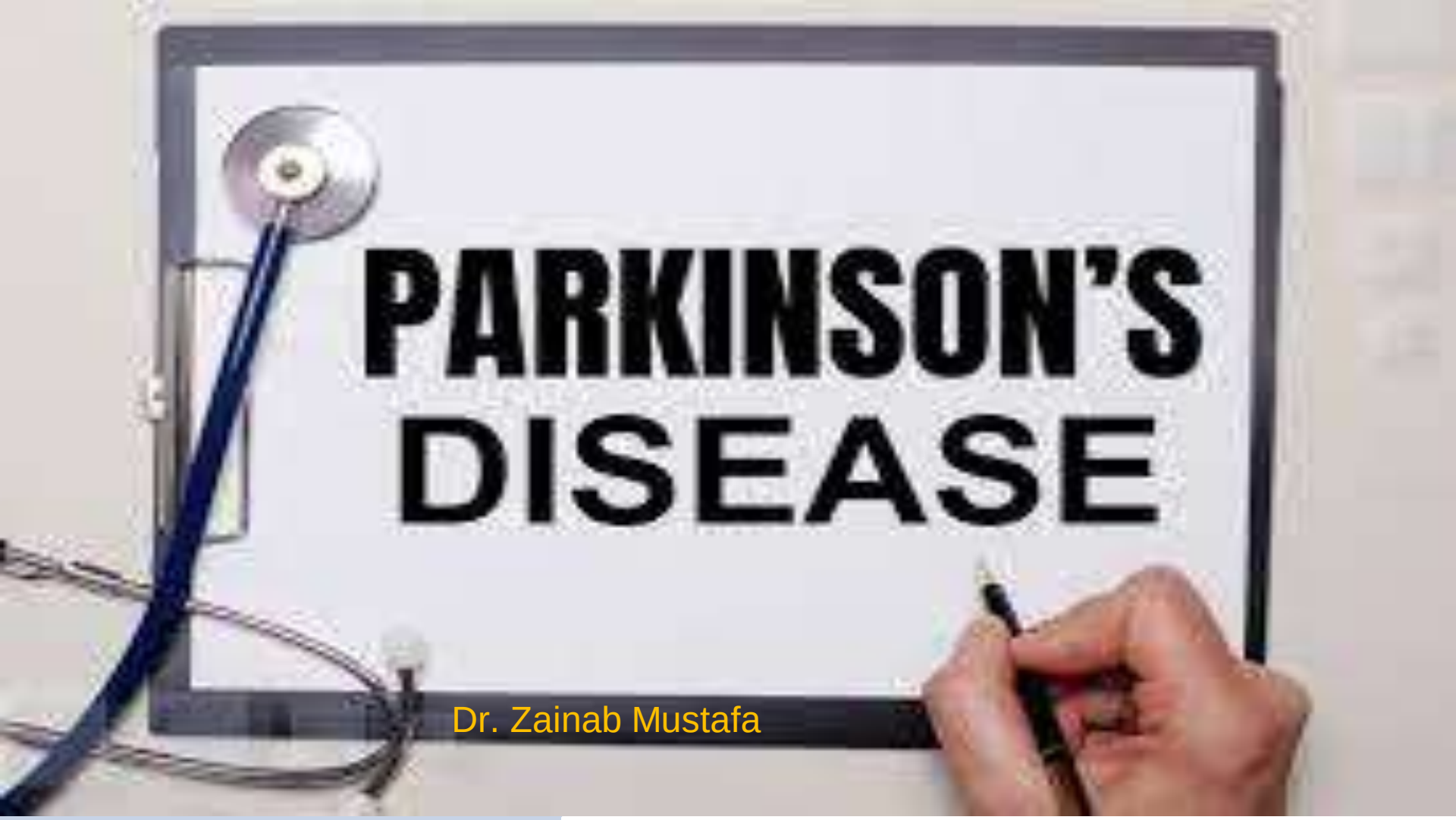


Dr. Zainab Mustafa

Parkinson disease

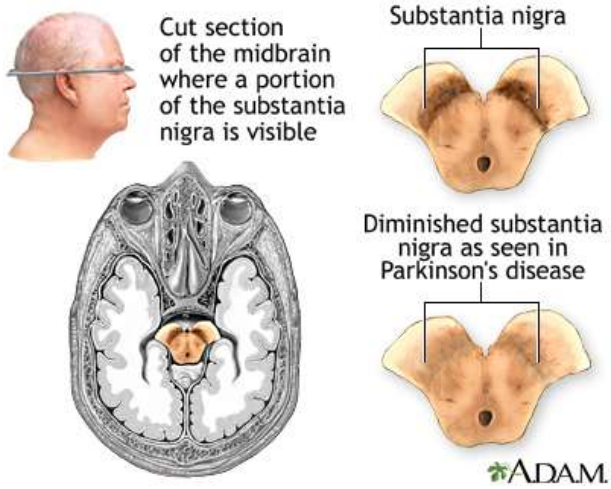
- **(PD)** has highly characteristic neuropathologic findings and a clinical presentation, including motor deficits and, in some cases, mental deterioration

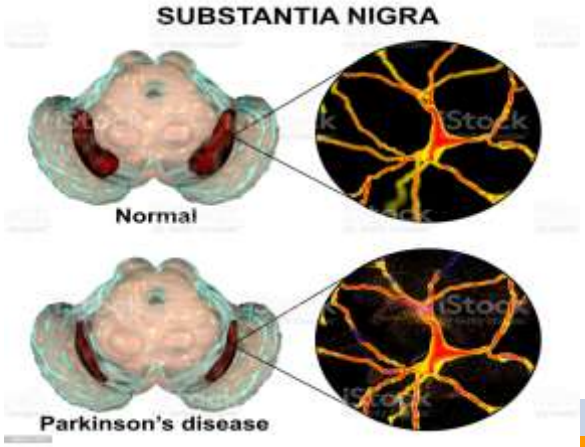
PATHOPHYSIOLOGY

The true etiology of PD is unknown.

Two hallmark features in the substantia nigra pars compacta are loss of neurons and presence of Lewy bodies. The degree of nigrostriatal dopamine loss correlates positively with severity of motor symptoms.

Reduced activation of dopamine1 and dopamine2 receptors results in greater inhibition of the thalamus and reduced activation of the motor cortex. Clinical improvement may be tied to restoring activity more at the dopamine2 receptor than at the dopamine1 receptor





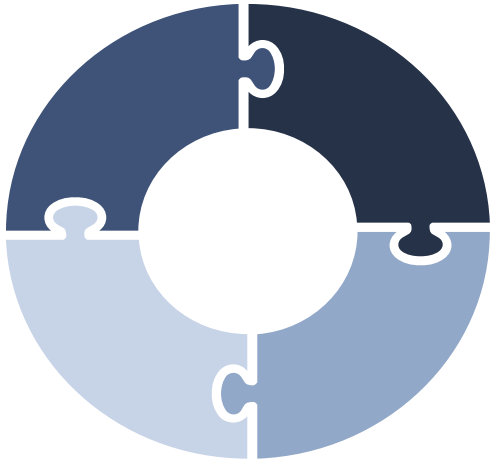
CLINICAL PRESENTATION

Signs and Symptoms

1. Cardinal signs

Akinesia or hypokinesia

Tremor



Rigidity

Posture or gait abnormalities

2. Secondary signs

Speech disturbances

Cognitive dysfunction

Micrographia

Autonomic dysfunction

Masked facies

Parkinson's Disease Symptoms

DIAGNOSIS

- The clinical diagnosis of PD is based on the presence of bradykinesia and at least one of the three other features:

muscular rigidity, resting tremor, and postural instability

- There are no laboratory tests available to diagnose PD, including genetic testing.
- Neuro-imaging may be useful for excluding other diagnoses.
- Medication history should be obtained to rule out drug-induced parkinsonism

Nonpharmacologic Therapy

- Surgery should be considered an adjunct to pharmacotherapy when patients are experiencing frequent motor fluctuations or disabling dyskinesia or tremor despite an optimized medical regimen .
- Other biotherapies, such as stem cell and gene-based approaches, are currently under investigation and remain highly experimental.

Pharmacologic Therapy

1.Monoamine Oxidase B Inhibitors

Three selective MAO-B inhibitors (rasagiline, safinamide, selegiline) are available for management of PD.
Rasagiline and selegiline contain a propargylamine moiety, which is essential for conferring irreversible ("suicide") inhibition of MAO-B, in contrast to safinamide, which is a reversible MAO-B inhibitor. At therapeutic doses, all three agents preferentially inhibit MAO-B over MAO-A.
Concomitant use of MAO-B inhibitors with meperidine and other selected opioid analgesics is contraindicated due to the small risk of serotonin syndrome. However, drugs with serotonergic antidepressants can be used concomitantly when clinically warranted.

As monotherapy in early PD, both selegiline and rasagiline provide modest improvements in motor function.
As add-on therapy, all three MAO-B inhibitors can provide up to 1 hour of extra “on” time for patients

Selegiline also increases the peak effects of levodopa and can worsen preexisting dyskinesias or psychiatric symptoms, such as delusions.
Metabolites of selegiline are L-methamphetamine and L-amphetamine. The oral disintegrating tablet may provide improved response and fewer side effects than the conventional formulation.

Both rasagiline and safinamide are well tolerated with minimal GI or neuropsychiatric side effects

2.Levodopa

Improvement in disability and possibly mortality

Greatest effect on bradykinesia and rigidity; less effect on tremor and postural instability

Carbidopa

Combined in fixed ratios with levodopa

Prevents some of the peripheral conversion of levodopa to dopamine by inhibiting peripheral dopamine decarboxylase; therefore, levodopa is available to cross the blood-brain barrier

75 mg/day is usually needed to inhibit peripheral decarboxylase activity.

Carbidopa/levodopa (Carbilev, Parcopa, Sinemet)

(a) High-protein diets decrease absorption.

(b) Immediate-release half-life 60–90 minutes

(c) Orally disintegrating tablet available; not absorbed sublingually

(d) Slow-release considerations: Fewer daily doses; less plasma fluctuations; delay to effect; cannot crush; can divide.

Acute adverse effects: Nausea and vomiting, orthostatic hypotension, cardiac arrhythmias, confusion, agitation, hallucinations

Long-term adverse effects: Wearing-off and on-off phenomena, involuntary movements (dyskinesias)

(a) Wearing-off phenomenon is the return of Parkinson disease symptoms before the next dose. Treatment of wearing-off includes adding a dopamine agonist, adding a MAO-B inhibitor, adding a catechol-*O*-methyl transferase inhibitor, or increasing the frequency or dose of levodopa.

(b) On-off phenomenon is a profound, unpredictable return of Parkinson disease symptoms without respect to the dosing interval. Treatment of on-off includes adding entacapone, rasagiline, pramipexole, ropinirole, apomorphine, or selegiline or redistributing dietary protein.

(c) Dyskinesias are drug-induced involuntary movements including chorea and dystonia. Treatment of dyskinesias includes decreasing the levodopa dose or adding amantadine as an antidyskinetic drug.

iv. Therapy initiation
(a) Standard formulation: 25 mg/100 mg 1 tablet orally three times daily; also available as orally disintegrating tablet
(b) Controlled-release formulation: 1 tablet orally two or three times daily
(c) Titration always necessary
(d) A combination of formulations may be needed (e.g., ½ tablet of Sinemet 25 mg/100 mg on awakening and 1 tablet of Sinemet CR 25/100 three times daily).

3.Anticholinergic Medications

Anticholinergic drugs (Trihexyphenidyl (Artane), benztropine (Cogentin))
Useful only for tremor and sometimes dystonic features in some patients, but they rarely substantially improve bradykinesia or other disabilities. They can be used as monotherapy or in conjunction with other antiparkinson drugs.

Anticholinergic side effects include dry mouth, blurred vision, constipation, and urinary retention. More serious reactions include forgetfulness, confusion, sedation, depression, and anxiety .Patients with preexisting cognitive deficits and the elderly are at greater risk for central anticholinergic side effects

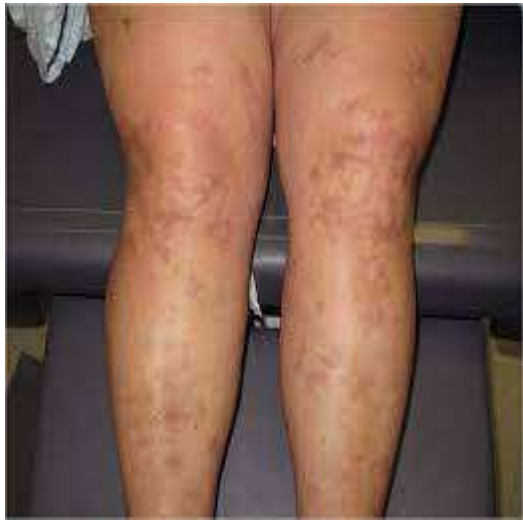
4.Amantadine

Amantadine often provides modest benefit for tremor, rigidity, and bradykinesia, but is most often used for levodopa-induced dyskinesia.

Dosing: 100 mg 1 tablet orally two or three times daily; caution in renal dysfunction

Doses should be reduced in patients with renal dysfunction (100 mg/day with creatinine clearances of 30–50 mL/min ,100 mg every other day for creatinine clearances of 15–29 mL/min

and 200 mg every 7 days for creatinine clearances less than 15 mL/min [0.25 mL/sec]) and those on hemodialysis.



Adverse effects include sedation, dry mouth, hallucinations, dizziness, and confusion. Livedo reticularis (a diffuse mottling of the skin in the upper or lower extremities) is a common but reversible side effect

5.Catechol-O -Methyltransferase Inhibitors

Tolcapone and entacapone are used in conjunction with carbidopa/levodopa to prevent the peripheral conversion of levodopa to dopamine (increasing the area under the curve of levodopa by approximately 35%).

Thus, “on” time is increased by approximately 1–2 hours, and dosage requirements of levodopa are decreased.

Avoid concomitant use of nonselective MAO inhibitors to prevent inhibition of the pathways for normal catecholamine metabolism.

Tolcapone’s use is limited by the potential for fatal liver toxicity, requiring strict monitoring of liver function. Reserve tolcapone for patients with fluctuations unresponsive to other therapies.

Because entacapone has a shorter half-life, 200 mg is given with each dose of carbidopa/levodopa up to eight times a day. Dopaminergic adverse effects may occur and are managed by reducing the carbidopa/levodopa dose. **Brownish orange urine** discoloration may occur (as with tolcapone), but hepatotoxicity is not reported with entacapone.

6.Dopamine Agonists

The ergot derivative bromocriptine and the nonergots pramipexole, rotigotine, and ropinirole are beneficial adjuncts in patients experiencing fluctuation in response to levodopa. They decrease the frequency of “off” periods and provide an levodopa-sparing effect.

Titrate the dose of dopamine agonists slowly to enhance tolerability, and find the least dose that provides optimal benefit .

The nonergots are safer and are effective as monotherapy in mild-to-moderate PD and as adjuncts to levodopa in patients with motor fluctuations.

There is less risk of developing motor complications from monotherapy with dopamine agonists than from levodopa. Because **younger** patients are more likely to develop **motor fluctuations**, **dopamine agonists are preferred** in this population. **Older patients** are more likely to **experience psychosis and orthostatic hypotension** from dopamine agonists; therefore, **carbidopa/levodopa may be the best** initial medication in elderly patients. For patients with cognitive problems or dementia, dopamine agonists are best avoided.

Adverse effects: Nausea, vomiting, postural hypotension, hallucinations, impulsive behaviors (e.g., hypersexuality, gambling, shopping, eating), falling asleep during activities of daily Living .
Other side effects include vivid dreams and sleep attacks. When added to levodopa, dopamine agonists may worsen dyskinesias. Hallucinations or delusions should be managed by dosage reduction or discontinuation and if needed addition of an atypical antipsychotic, such as clozapine, quetiapine, or pimavanserin (FDA approved for psychosis in PD).

Bromocriptine is not commonly used because of its safety profile, which includes a risk of pulmonary fibrosis.

Pramipexole is primarily renally excreted, and the initial dose must be adjusted in renal insufficiency. A once-daily extended-release formulation is available.

Ropinirole is metabolized by cytochrome P4501A2; fluoroquinolones and smoking may alter ropinirole clearance. A once-daily formulation is available.

Rotigotine patch provides continuous release over 24 hours, and disposition is not affected by hepatic or renal impairment.

Apomorphine is a nonergot dopamine agonist given as a subcutaneous “rescue” injection. For patients with advanced PD with intermittent “off” episodes despite optimized therapy, subcutaneous apomorphine triggers an “on” response within 20 minutes, and duration of effect is up to 100 minutes. Most patients require 0.06 mg/kg. Prior to injection, patients should be premedicated with the antiemetic trimethobenzamide. It is contraindicated with the serotonin-3-receptor blockers (eg, ondansetron).