

Parkinson Disease

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Incidence, Prevalence, and Epidemiology

Parkinson Disease (PD) is a chronic, *progressive* movement disorder first described in 1817 by Dr. James Parkinson.

Since that time, the term *parkinsonism* has come to refer to any disorder associated with *two or more features* of tremor, rigidity, bradykinesia, or postural instability.



Incidence, Prevalence, and Epidemiology

Most cases of PD are of unknown cause and referred to as **idiopathic** parkinsonism; however, *viral* encephalitis, *cerebrovascular* disease, and *hydrocephalus* have symptoms similar to PD as part of their clinical presentation.



Incidence, Prevalence, and Epidemiology

PD age of onset is variable, increasing after age 50 and *peaking around age 80*.

Males have higher incidence rates than females.

Despite the availability of effective symptomatic treatments to improve both quality of life and life expectancy, **no cure** exists.

Incidence, Prevalence, and Epidemiology

The symptoms of PD are *progressive*, and within 10 to 20 years, significant **immobility** results for most patients.

PD itself does not cause **death**; however, patients often succumb to *complications* related to impaired mobility and function (e.g., aspiration pneumonia, thromboembolism) and overall frailty.

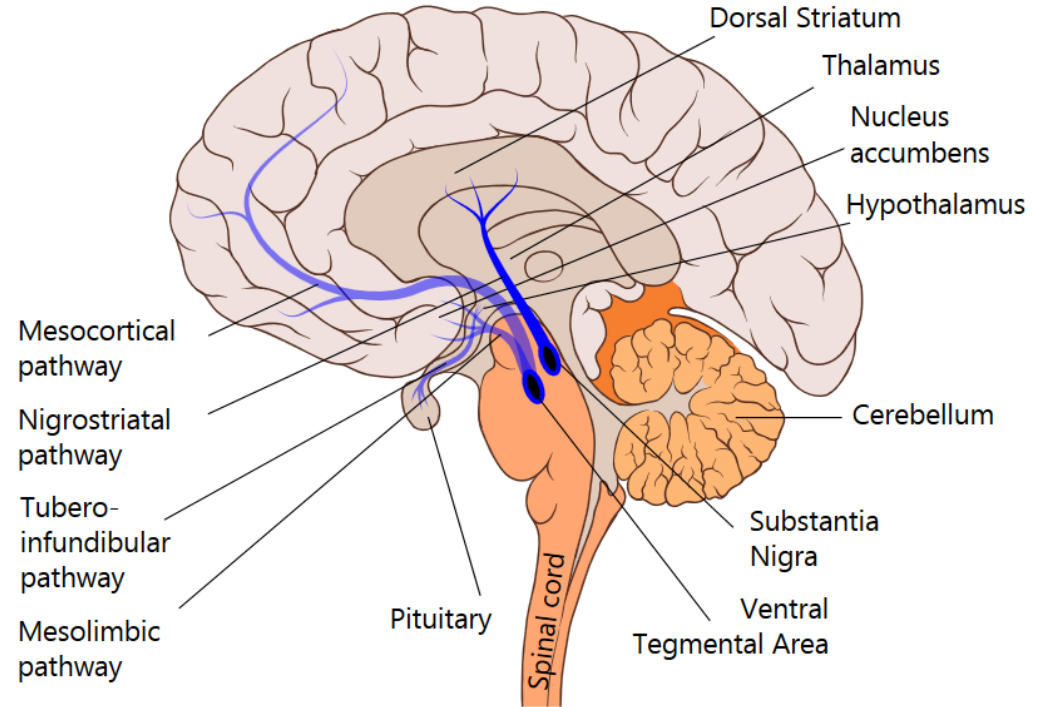


Etiology

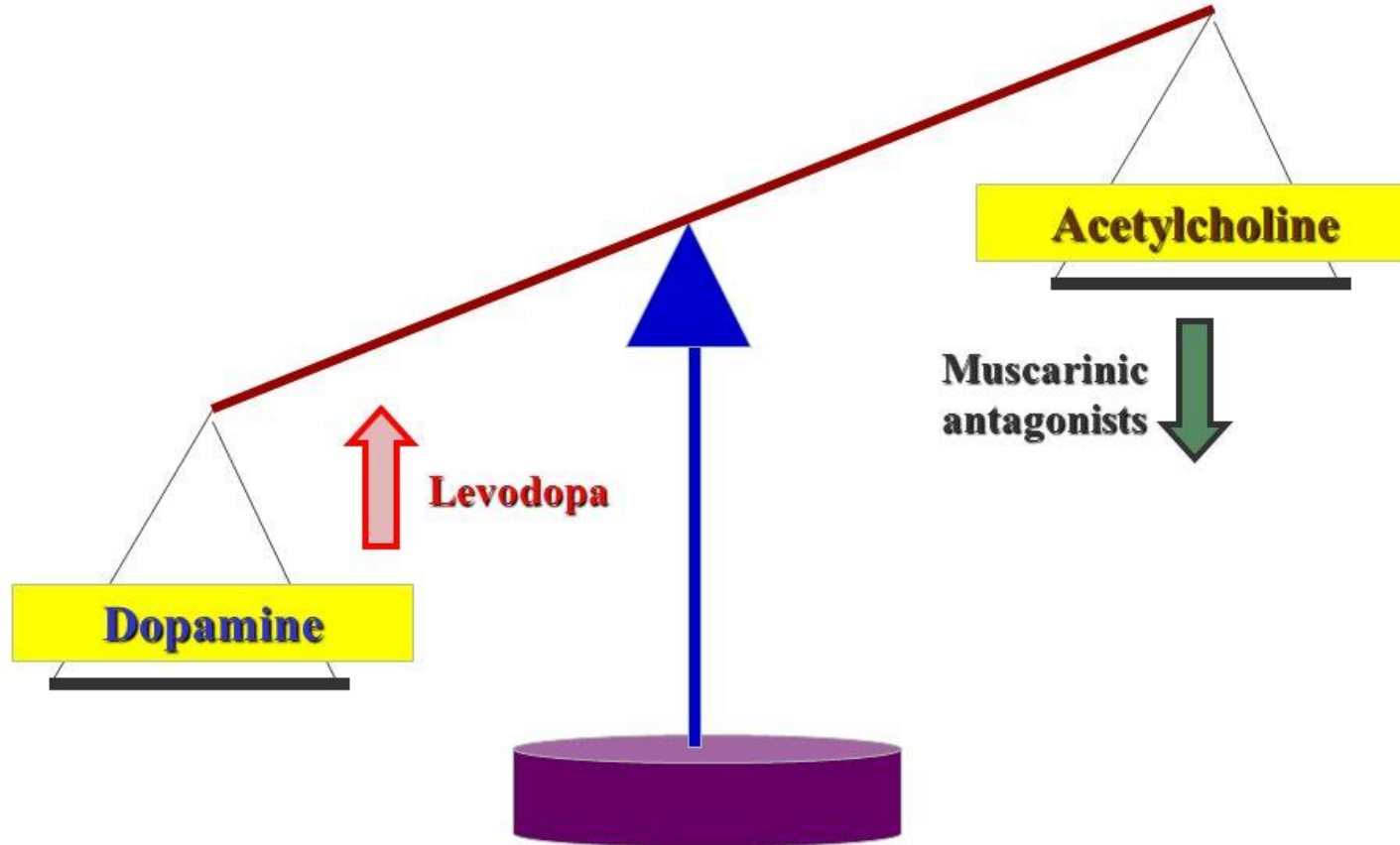
The *relative contributions* of environment and genetics to the occurrence of PD remain controversial; rural living, pesticide exposure, and consumption of well water have consistently been associated with increased lifetime risk of PD, whereas *exercise, cigarette smoking and caffeine* ingestion appear to be **protective**.

Pathophysiology

The salient features of PD result from a **loss of dopaminergic neurons** in the *nigrostriatal* tracts of the brain and development of abnormal intraneuronal protein aggregates called *Lewy bodies* that interfere with neuronal function.



**Abnormal balance of DA/ACh neuronal functions
in extrapyramidal system of Parkinson disease**



Clinical Presentation of Parkinson Disease

The **diagnosis** of PD remains firmly grounded in obtaining a careful *history* and *physical examination*. The neurologic examination to assess motor function, along with a positive response to levodopa, is highly diagnostic.



Clinical Presentation of Parkinson Disease

It is important to note that *not all classic features* are required to make the diagnosis of PD. The presence of **two or more features** indicates clinically probable PD.

Tremor, which is most often the first symptom observed in younger patients, is usually *unilateral on initial presentation*.

Clinical Presentation of Parkinson Disease

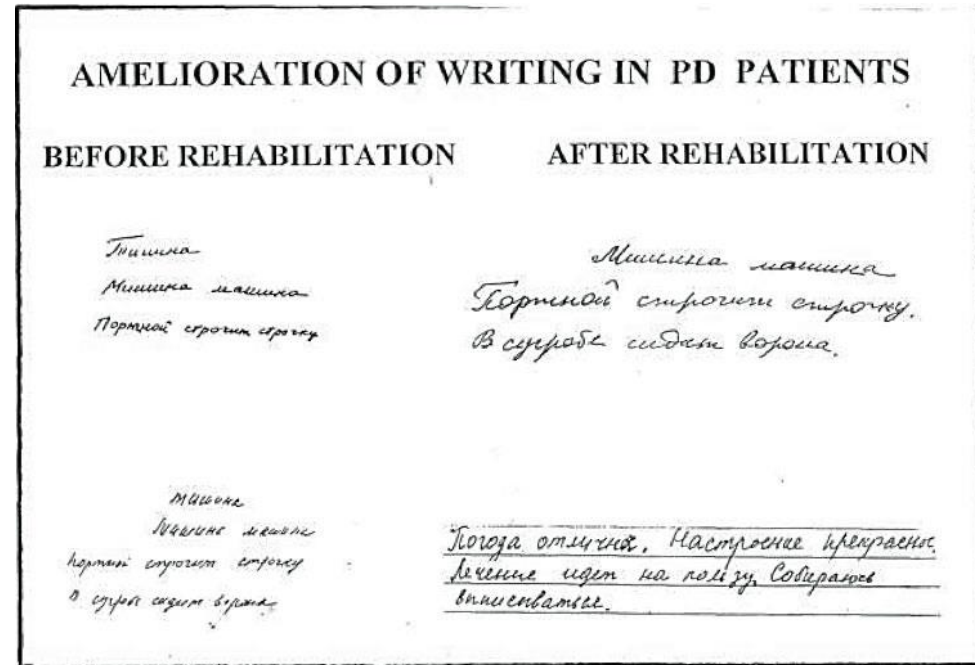
Symptoms that were *unilateral on initial* presentation progress asymmetrically and often become **bilateral** and more severe with disease progression.

Patients with PD may develop *masked faces*, or a blank stare with reduced eye blinking.



Clinical Presentation of Parkinson Disease

Handwriting abnormalities occur frequently, particularly micrographia, a symptom of bradykinesia.



Motor features of Parkinson disease

Cardinal manifestations
Tremor
Bradykinesia
Rigidity
Postural instability
Other motor features
Craniofacial
Hypomimia (masked facial expression)
Decreased eye blinking
Speech disturbances (hypokinetic dysarthria, hypophonia)
Dysphagia
Sialorrhea
Visual
Blurred vision
Impaired contrast sensitivity
Hypometric saccades
Impaired vestibuloocular reflex
Impaired upward gaze and convergence
Lid apraxia
Musculoskeletal
Micrographia
Dystonia
Myoclonus
Stooped posture
Camptocormia (severe anterior flexion of the thoracolumbar spine)
Pisa syndrome (subacute axial dystonia with lateral flexion of the trunk, head, and neck)
Kyphosis
Scoliosis
Difficulty turning in bed
Gait
Shuffling, short-stepped gait
Freezing
Festination

Clinical Presentation of Parkinson Disease

Drugs may also mimic idiopathic PD.

Drugs that act as **antagonists** at dopaminergic **D₂ receptors** (e.g., neuroleptics, prochlorperazine, and metoclopramide), and others such as valproate, amiodarone, phenytoin, and lithium may cause a state of drug-induced parkinsonism.

Staging of Parkinson Disease

Staging of Disability in Parkinson Disease

Stage 1	Unilateral involvement only; changes in posture, walking, and facial expressions occur; minimal or no functional impairment
Stage 2	Bilateral involvement, without impairment of balance; walking problems and poor posture may be apparent
Stage 3	Evidence of postural imbalance and slowness of movement; some restriction in activities; capable of leading independent life; mild-to-moderate disability such as dressing and eating
Stage 4	Severely disabled, possibility can stand without assistance but cannot walk and stand unassisted; significantly incapacitated required help needed for activities of daily living and is unable to live alone
Stage 5	Stiffness in the legs making it impossible to stand or walk; restricted to bed or wheelchair unless aided; experience hallucinations and delusion where both motor and nonmotor symptom management are needed

Source: Ascherio A, Schwarzschild MA. The epidemiology of Parkinson's disease: risk factors and prevention. *Lancet Neurol.* 2016;15(12):1257–1272.

Treatment of Parkinson Disease

Patients in early PD stages should be enrolled in *rehabilitative services* to improve balance and motor function. These therapies include exercise, physical and occupational therapy, yoga, and speech therapy.

Additionally, **dietary recommendations** of increased protein and vitamin D can be beneficial at the earlier stages to increase strength and enhance well-being and mood.

Treatment of Parkinson Disease

Psychological support is often necessary in dealing with depression and other related problems.

Treatment of Parkinson Disease

Drug therapy for the disease is aimed primarily at **replenishing the supply** of dopamine.

This is accomplished through one, or a combination, of the following methods:

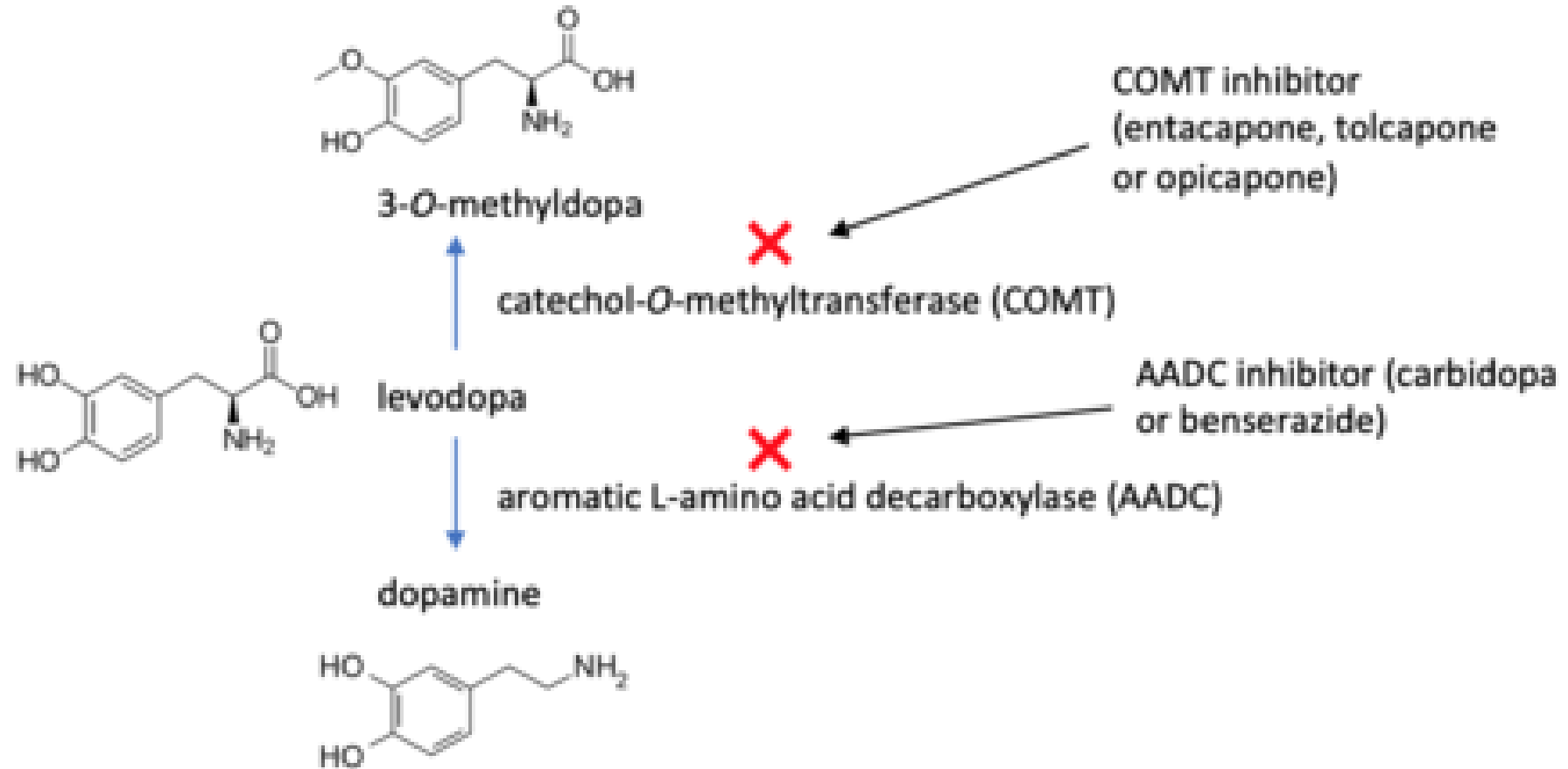
- (a) Administering *exogenous dopamine* in the form of a precursor, levodopa;
- (b) *Stimulating dopamine receptors* within the striatum through the use of dopamine agonists (e.g., pramipexole, ropinirole); or
- (c) *Inhibiting the major metabolic pathways* within the brain that are responsible for the degradation of levodopa and its metabolites.

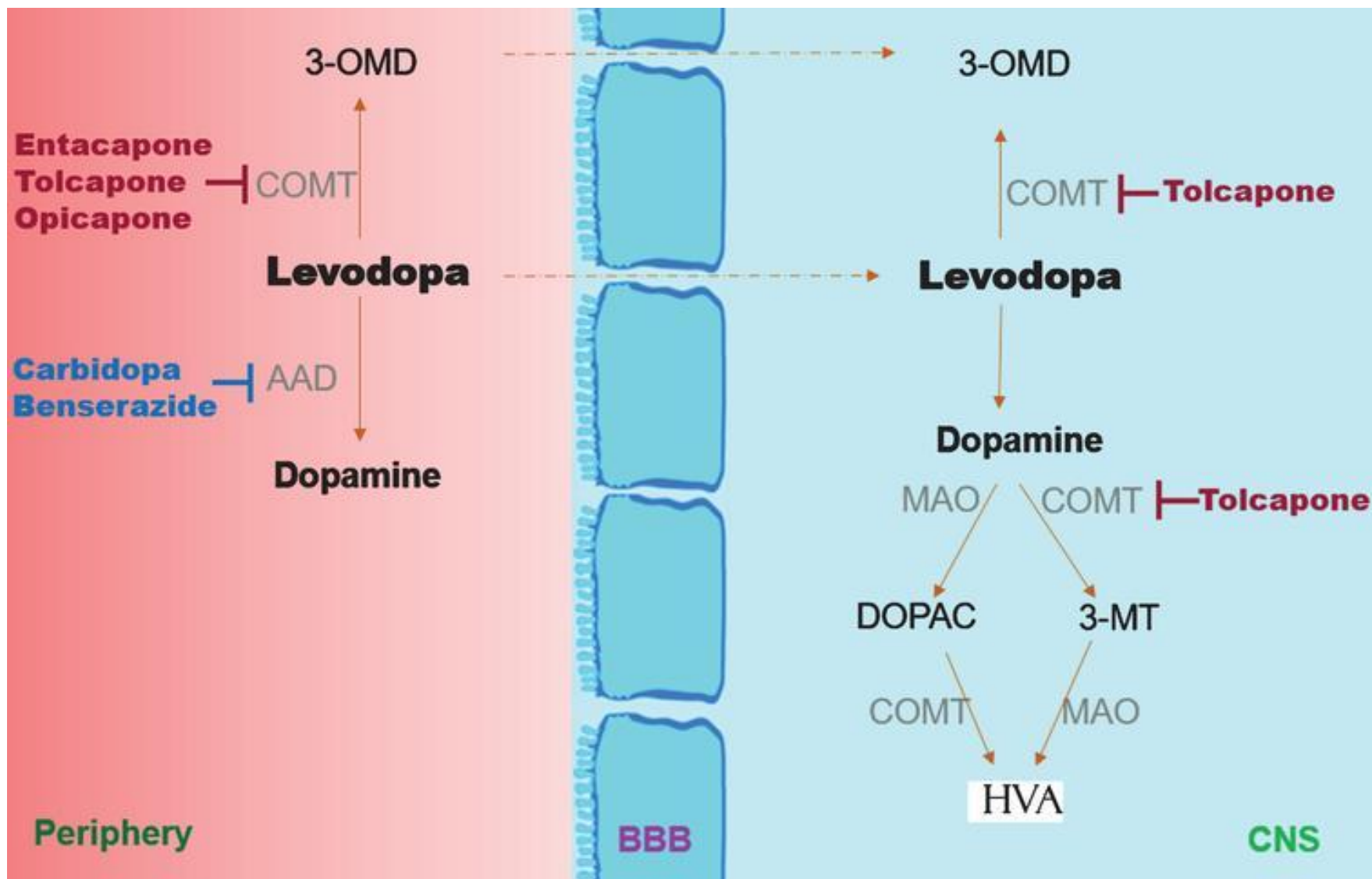
Treatment of Parkinson Disease

This latter effect is achieved through the use of aromatic L-amino acid decarboxylase (**AAD**) inhibitors (e.g., carbidopa), **COMT** inhibitors (e.g., entacapone), or **MAO-B** inhibitors (e.g., selegiline).

Anticholinergics are also used; however, they are solely efficacious for the cholinergic-mediated **tremor**, and their routine use is limited by central nervous system (CNS) *adverse effects*, particularly in older patients.







Treatment of Parkinson Disease

A unique agent, **amantadine**, is also used occasionally and may provide modest benefits via both dopaminergic and non-dopaminergic (inhibition of glutamate) mechanisms.

Despite optimization of both pharmacologic and non-pharmacologic therapies in PD, *physical disability* is **progressive** and unavoidable.



Treatment of Parkinson Disease

Generic (Trade) Name	Dosage Unit	Titration Schedule	Usual Daily Dose	Adverse Effects
Amantadine (Symmetrel®)	100-mg capsule and tablet Liquid: 50 mg/5 mL 68.5- and 137-mg ER capsule 129-, 193-, and 258-mg ER tablet	IR capsule, tablet, liquid: 100 mg every day; increased by 100 mg every 1–2 weeks ER capsule: 137 mg every day; increased by 137 mg every week ER tablet: 129 mg every day; increased by 129 mg every week	IR capsule, tablet, liquid: 100–400 mg ER capsule: 274 mg ER tablet: 129–322 mg	Orthostatic hypotension, insomnia, depression, hallucinations, livedo reticularis, xerostomia
Anticholinergic agents				
Trihexyphenidyl (Artane)	2- and 5-mg tablets Liquid: 2 mg/5 mL	1–2 mg/day increased by 1–2 mg every 3–5 days	6–10 mg divided tid to qid	Constipation, xerostomia, dry skin, dysphagia, confusion, memory impairment

Treatment of Parkinson Disease

Generic (Trade) Name	Dosage Unit	Titration Schedule	Usual Daily Dose	Adverse Effects
<i>Combination agents</i>				
Carbidopa–levodopa (IR)/entacapone (Stalevo®)	12.5-/50-/200-, 18.75-/75-/200-, 25-/100-/200-, 31.25-/125-/200-, 37.5-/150-/200-, 50-/200-/200-mg tablets	Titrate with individual dosage forms (carbidopa/levodopa and entacapone) first, then switch to combination tablet	Varies (see individual drugs)	See individual drugs; <70–100 mg daily of carbidopa component may experience nausea and vomiting
<i>Dopamine replacement</i>				
Carbidopa–levodopa (IR) (Sinemet®)	10-/100-, 25-/100-, and 25-/250-mg tablets	25/100 mg bid, increased by 25/100 mg weekly to effect and as tolerated	30/300 to 150/1500 mg divided tid to qid	Nausea, orthostatic hypotension, confusion, dizziness, hallucinations, dyskinesias, blepharospasm
Carbidopa–levodopa (CR) (Sinemet® CR)	25-/100- and 50-/200-mg tablets	25/100 mg bid (spaced at least 6 hours apart), increased every 3–7 days	50/200 to 500/2000 divided qid	Same as regular Sinemet®

Treatment of Parkinson Disease

Generic (Trade) Name	Dosage Unit	Titration Schedule	Usual Daily Dose	Adverse Effects
<i>Dopamine agonists</i>				
Bromocriptine (Parlodel®)	2.5-mg tablet, 5-mg capsule	1.25 mg bid, titrate slowly as tolerated (2.5 mg/day every 2–4 weeks)	10–40 mg divided tid; max 100 mg/day	Orthostatic hypotension, confusion, dizziness, hallu- cinations, nausea, muscle cramps; retroperitoneal, pleural, pericardial fibrosis; cardiac valve thickening
Pramipexole (Mirapex®, Mirapex® ER)	IR: 0.125-, 0.25-, 0.50-, 0.75-, 1-, 1.5-mg tablets ER: 0.375-, 0.75-, 1.5-, 2.25-, 3-, 3.75-, 4.5- mg tablets	IR: 0.375 mg divided tid; titrate 5 to 7 days by 0.125–0.25 mg/dose ER: 0.375 mg once daily; titrate 5–7 days by 0.75 mg/dose	Immediate release: 1.5–4.5 mg divided tid ER: 1.5–4.5 mg once daily	Orthostatic hypotension, con- fusion, dizziness, hallucina- tions, nausea, somnolence
Ropinirole (Requip, Requip XL)	0.25-, 0.5-, 1-, 2-, 3-, 4-, 5-mg tablet XL: 2-, 4-, 6-, 8-, 12-mg tablets	0.25 mg tid; titrate weekly by 0.25 mg/dose XL: 2 mg once daily; titrate weekly or longer intervals by 2 mg/day	3–24 mg divided tid XL: 3–24 mg once daily	Orthostatic hypotension, con- fusion, dizziness, hallucina- tions, nausea, somnolence

Treatment of Parkinson Disease

Generic (Trade) Name	Dosage Unit	Titration Schedule	Usual Daily Dose	Adverse Effects
<i>Catechol-O-methyltransferase inhibitors</i>				
Entacapone (Comtan®)	200-mg tablet	200 mg with each administration of carbidopa/levodopa, up to 1600 mg daily	600–1600 mg daily	Diarrhea, dyskinesias, abdominal pain, urine discoloration
<i>Monoamine oxidase type B inhibitors</i>				
Selegiline (El-depryl®) ^b	5-mg tablet, capsule	5 mg every morning; may increase to 5 mg bid (5 mg with breakfast and 5 mg with lunch)	5–10 mg/day	Insomnia, dizziness, nausea, vomiting, xerostomia, dyskinesias, mood changes; use caution when coadministered with sympathomimetics or serotonergic agents (increased risk of serotonin syndrome); avoid tyramine-containing foods

Treatment of Early Parkinson Disease

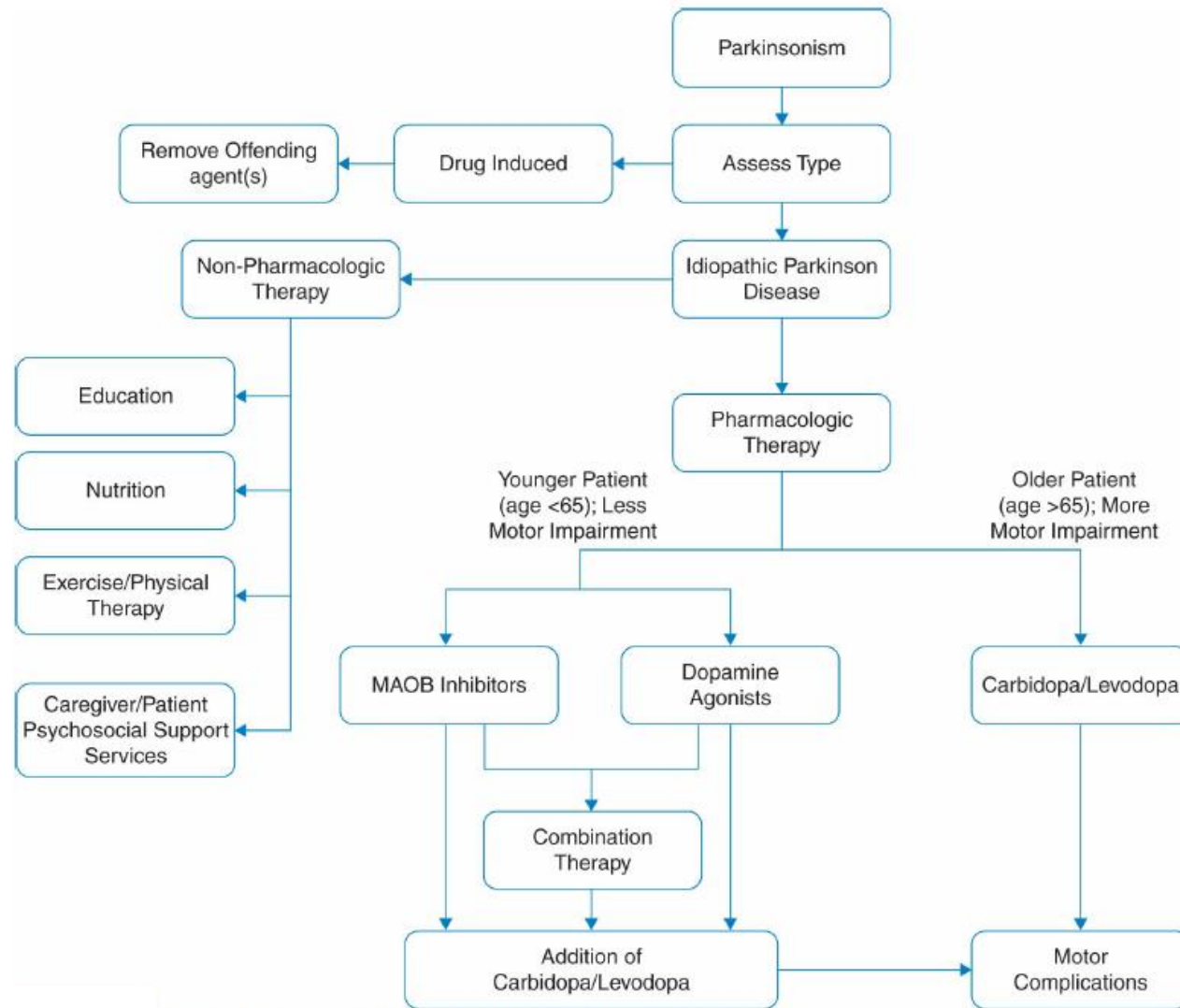
Despite advances in pharmacologic treatment options for PD, **no therapy** has been proven to be *disease-modifying or neuroprotective*.

Therapy continues to be *symptomatic*, and **levodopa** remains the *most effective* antiparkinsonian agent. With long-term use, the *efficacy of levodopa decreases* and risk for the development of *motor fluctuations* and *dyskinesias* increases.

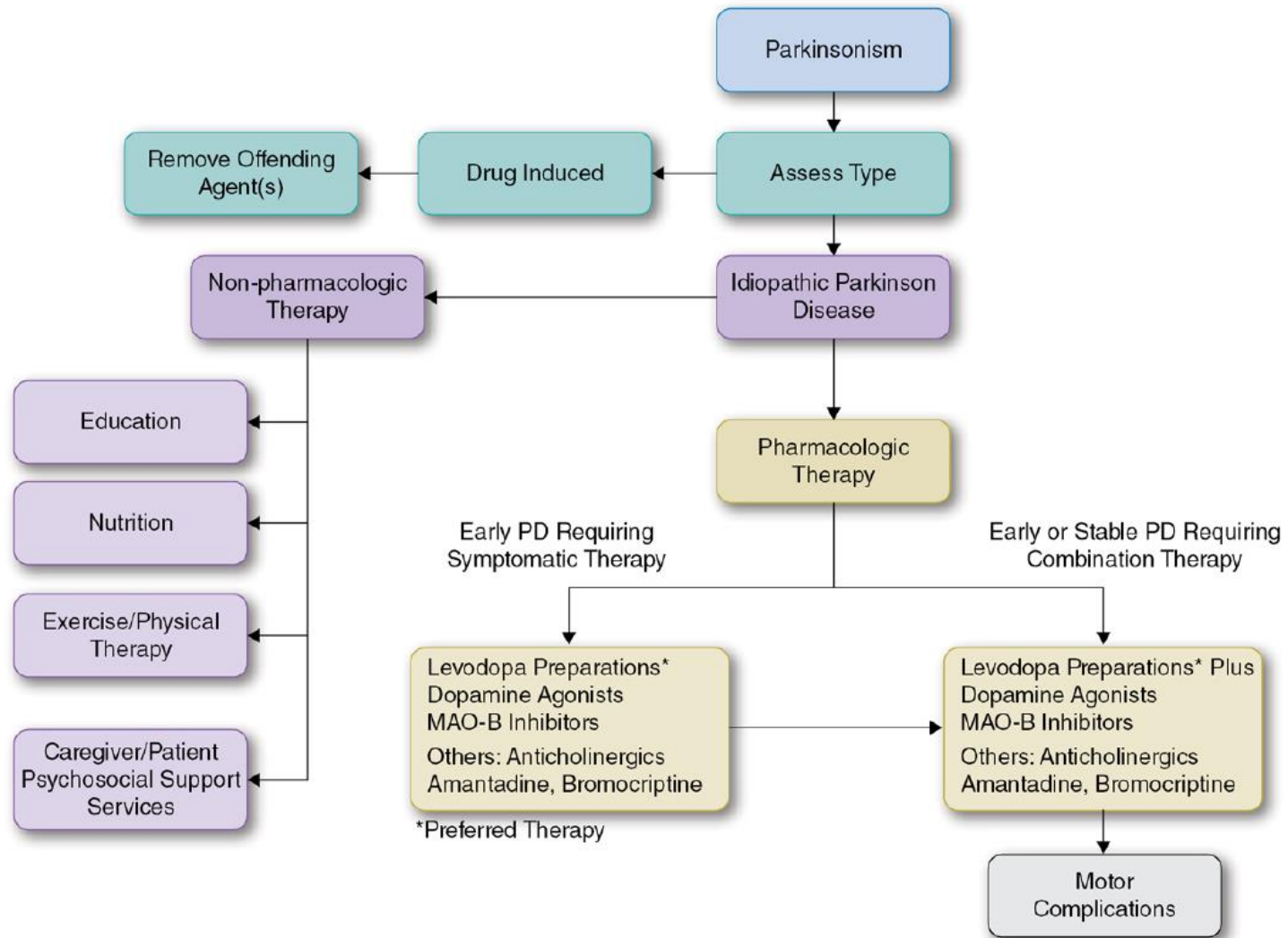
Treatment of Early Parkinson Disease

Although no consensus has been reached about **when to initiate** symptomatic treatment, most healthcare professionals agree that treatment should begin when the patient begins to experience *functional impairment* as defined by:

- (a) Threat to employment status,
- (b) Symptoms affecting the dominant side of the body, or
- (c) Bradykinesia or rigidity.



Suggested treatment algorithm for the management of early PD.



Treatment of Early Parkinson Disease

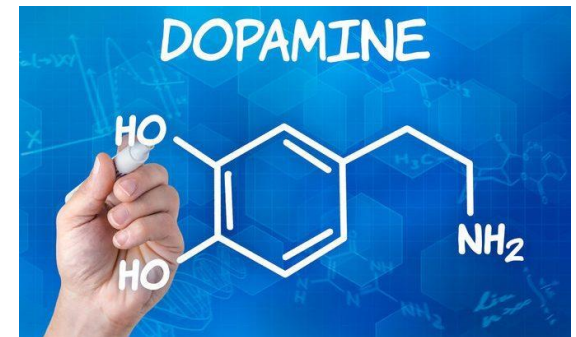
Although *dopamine agonists* are **not** as effective as levodopa, the dopamine agonists have *potential advantages*.

- Unlike levodopa, circulating *plasma amino acids* do **not** compete with dopamine agonists for absorption and transport into the brain, eliminating *administration constraints*.
- Dopamine agonists have a *longer half-life* than levodopa formulations, reducing the need for multiple daily dosing.

Treatment of Early Parkinson Disease

Dopamine Agonists

Two generations of dopamine agonists have been used for the treatment of idiopathic PD, in early-stage PD as monotherapy, or as an adjunct to levodopa in patients with advanced disease.



Treatment of Early Parkinson Disease

The *first-generation* dopamine agonists, which are derived from ergot alkaloids, include bromocriptine, pergolide, and cabergoline.

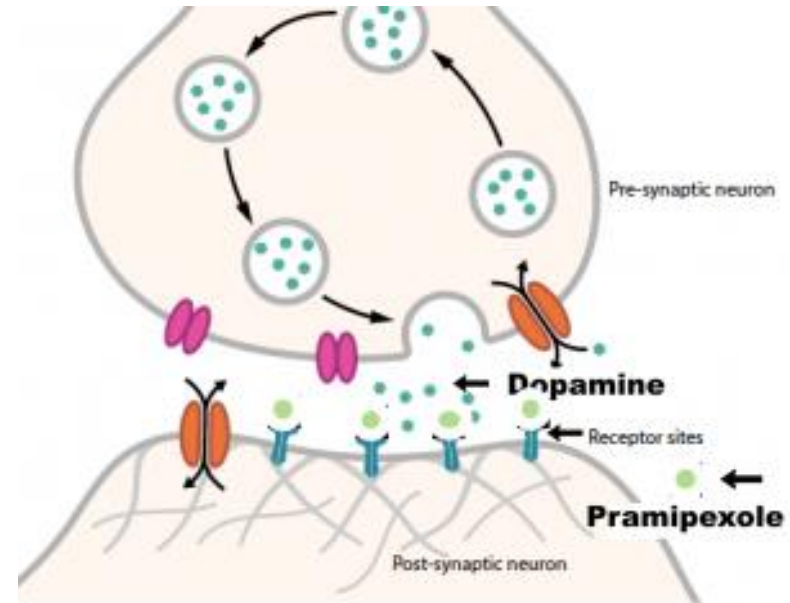
These older agents are now rarely used because of increased risk of retroperitoneal, pleural, and pericardial **fibrosis**, as well as a two- to four-fold increased risk for *cardiac valve fibrosis* when compared with non-ergoline dopamine agonists and controls.



Treatment of Early Parkinson Disease

Pramipexole, ropinirole, and apomorphine are *second-generation* nonergoline dopamine agonists.

Dopamine agonists work by *directly stimulating* postsynaptic dopamine receptors within the striatum.



Treatment of Early Parkinson Disease

Adverse Effects

In studies of patients with early-stage disease, the most common side effects were nausea, dizziness, somnolence, insomnia, constipation, asthenia, hallucinations, and leg edema.

The most common reasons for *discontinuing* these agents are **mental disturbances** (e.g., nightmares, confusion, hallucinations, insomnia) and orthostatic hypotension.

Treatment of Early Parkinson Disease

Sudden, excessive **daytime** *somnolence*, including while driving, has been reported with dopamine agonists and has resulted in accidents.

Affected patients did **not** always report *warning signs* before falling asleep and believed they were alert immediately before the event.



Treatment of Early Parkinson Disease

Labeling for these drugs includes a **warning** that patients should be alerted to the possibility of falling asleep while engaged in daily activities.

Patients should be advised to *refrain from driving or other potentially dangerous activities* until they have **gained sufficient experience** with the dopamine agonist to determine whether it will hinder their mental and motor performance.

Treatment of Early Parkinson Disease

Dopamine agonist therapy in patients with PD is associated with 2- to 3.5-fold increased odds of developing an **impulse control** disorder.

These cases may represent variations of a behavioral syndrome termed *dopamine dysregulation syndrome*.



Treatment of Early Parkinson Disease

Features of the syndrome have been reported, including pathologic gambling, punding (carrying out repetitive, purposeless motor acts), hypersexuality, walkabout (having the urge to walk great distances during on-times, often with no purpose or destination and abnormalities in time perception), compulsive buying, binge eating, drug hoarding, and social independence or isolation.



Treatment of Early Parkinson Disease

The syndrome appears to be *more common* among **younger, male** patients with early-onset PD, as well as those having novelty-seeking personality traits, depressive symptoms, and current use of alcohol or tobacco.

Treatment of Early Parkinson Disease

Management of impulse control disorders can be challenging, because it often requires *modification of dopaminergic therapies*, which must be carefully **balanced** with the accompanying *risk of worsening* motor function.

- Underlying depression, if present, should be treated and may improve impulse control.
- Non-pharmacologic measures (such as limiting access to money or the Internet) may be helpful; in some cases, antipsychotic drugs may be considered, but must also be used carefully to avoid precipitating motor disability.

Treatment of Early Parkinson Disease

Lastly, it should be noted that the *abrupt discontinuation* of dopamine agonists and levodopa may precipitate the development of a withdrawal syndrome similar to neuroleptic malignant syndrome (NMS).

This NMS-like syndrome known as parkinsonism hyperreflexia syndrome can lead to symptoms of hyperthermia, muscle rigidity, hyperreflexia, mental status changes, autonomic instability (eg, tachycardia, tachypnea, and blood pressure fluctuations), and laboratory changes.

Treatment of Early Parkinson Disease

Monoamine Oxidase-B Inhibitors

The monoamine oxidase-B inhibitors are irreversible inhibitors of MAO-B, a major enzymatic pathway responsible for the metabolism of dopamine in the brain, and inhibition increases the amount of striatal dopamine.

Treatment of Early Parkinson Disease

Selegiline

The usual dosage of conventional selegiline is 10 mg/day administered as 5 mg in the *morning* and *early afternoon*.

It is not given in the evening because excess stimulation from *metabolites* (L-methamphetamine and L-amphetamine) can cause **insomnia** and other psychiatric side effects.

Treatment of Early Parkinson Disease

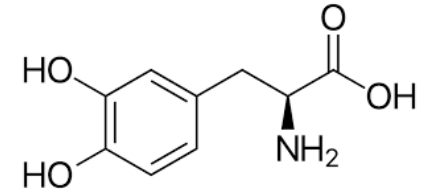
Adverse Effects

The most common adverse effects include nausea, dizziness, headache, and dry mouth. **CNS effects** such as hallucinations, vivid dreams, and confusion also occur but at a lower rate as compared with dopamine agonists.

Treatment of Early Parkinson Disease

Levodopa

Dopamine itself *does not cross* the blood–brain barrier. Levodopa, a dopamine precursor with *no known* pharmacologic *action* of its own, crosses the blood–brain barrier, where it is converted by the enzyme aromatic amino acid (dopa) decarboxylase to dopamine.



Treatment of Early Parkinson Disease

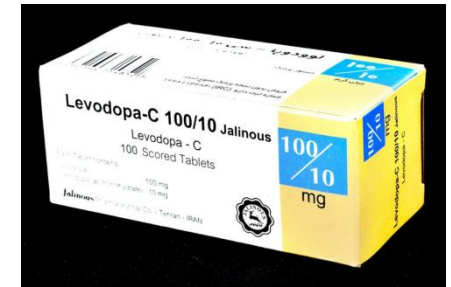
Because significant amounts of levodopa are **peripherally** (extracerebrally) *metabolized* to dopamine by dopa decarboxylase, *extremely high doses* are necessary if administered alone.

For this reason, levodopa is always *co-administered* with a dopa decarboxylase inhibitor. This allows the dose of levodopa to be decreased by 75%.

Treatment of Early Parkinson Disease

By combining levodopa with a *dopa decarboxylase* inhibitor that **does not penetrate** the blood–brain barrier, a decrease in the peripheral conversion of levodopa to dopamine can be achieved, whereas the desired conversion within the striatum remains unaffected.

A fixed combination of carbidopa and levodopa is available in ratios of 1:4 (carbidopa/levodopa 25/100) and 1:10 (carbidopa/levodopa 10/100 and 25/250).



Treatment of Early Parkinson Disease

Dosing

About 70 to 100 mg/day of carbidopa is necessary to saturate peripheral dopa decarboxylase. It is usually **unnecessary** and more costly to administer carbidopa in *higher amounts*.

Therapy should be initiated with *immediate-release* carbidopa/levodopa 25 mg/100 mg 3 times a day. The immediate-release formulation is preferred because it allows for much *easier dose adjustment*.

Treatment of Early Parkinson Disease

When levodopa doses *exceed* 750 mg/day, the patients can be **switched** from the 1:4 ratio of carbidopa/levodopa to the 1:10 ratio to prevent providing excessive amounts of decarboxylase inhibitor.

Treatment of Early Parkinson Disease

Patients should be instructed to take immediate-release carbidopa/levodopa *30 minutes before or 60 minutes after meals* for optimal efficacy.

If **nausea** develops and *administration with food* is considered, a low protein meal should be encouraged.

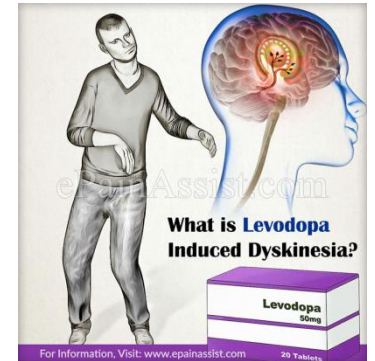


Treatment of Early Parkinson Disease

Adverse Effects

Although levodopa is the most effective agent for PD, it is associated with **many** undesirable side effects, such as nausea, vomiting, and anorexia, postural hypotension, and cardiac arrhythmias.

In addition, **mental disturbances** are encountered in 15% of patients, and abnormal involuntary movements (*dyskinesias*) can be seen in up to 55% of patients during the first 6 months of levodopa treatment.



Treatment of Early Parkinson Disease

Psychiatric side effects are associated with levodopa therapy and include confusion, depression, psychosis, hypomania, and vivid dreams.

Advancement of the **PD itself** correlates with *cognitive decline* and greater frequency of CNS findings, possibly mediated through an underlying Lewy body pathology. In some situations, it may be *difficult to separate* the respective drug from disease effects.

Treatment of Early Parkinson Disease

Some patients receiving levodopa experience **psychomotor excitation** (eg, overactivity, restlessness, agitation). Similarly, **hypomania** has been reported in up to 8% of patients and is characterized by grandiose thinking, flight of ideas, tangential thinking, and poor social judgment.

Normal sexual activity often is *restored* with improved motor function; however, hypersexuality and libido are increased in about 1% of levodopa-treated patients.

Treatment of Early Parkinson Disease

Anticholinergics

Currently, they are used to specifically target **tremor**.

Anticholinergic drugs such as benztropine and trihexyphenidyl work by blocking the excitatory neurotransmitter *acetylcholine* in the striatum, which minimizes the effect of the relative increase in cholinergic sensitivity.



Treatment through the Progression of Parkinson Disease

Motor Complications

Though variable, the *initial levodopa response* period may **last up to 5 years**. After this initial period of stability, 50% to 90% of patients receiving levodopa for 5 or more years will eventually experience *motor complications*.

Motor complications may present as periods of either too much (**dyskinetic**) dopaminergic activity, too little (**akinetic**) dopaminergic activity, or in **combination**.

Treatment through the Progression of Parkinson Disease

Peak-dose dyskinesias, brief, irregular and jerky movements, are the *most common form of dyskinesias* that occur with chronic levodopa (and sometimes dopamine agonist) therapy.

These symptoms frequently **subside** at the *end of the dosing* interval because levodopa levels fall.



Treatment through the Progression of Parkinson Disease

If peak-dose dyskinesias occur, the following strategies should be considered:

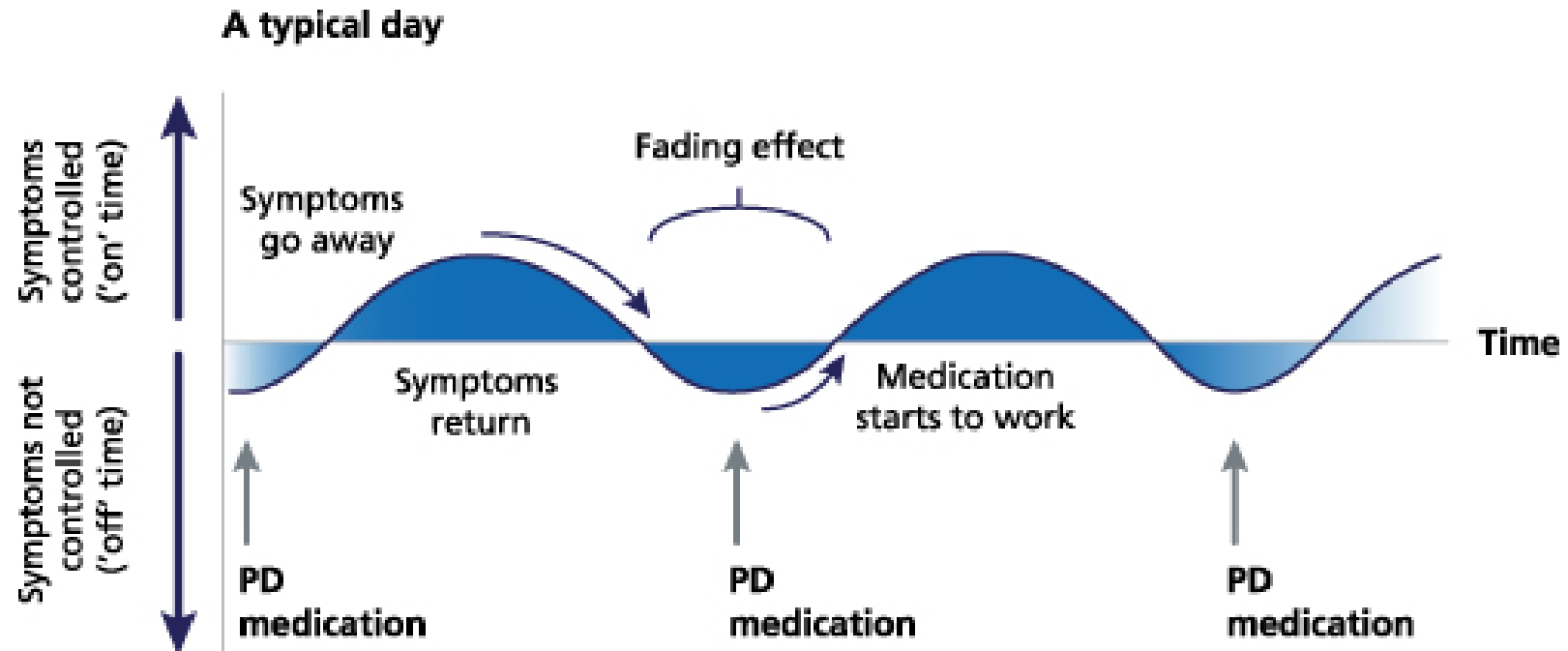
1. The levodopa *dose can be lowered* but given *more frequently*.
2. Agents that *prolong the half-life* of levodopa but do not provide stable levodopa plasma concentrations (e.g., COMT inhibitor, MAO-B inhibitor) can be added.
3. Consideration can be given to *switching patients to IR tablets* if taking modified-release formulations of carbidopa/levodopa (for ease in refining dose adjustments).
4. An **antidyskinetic** agent such as *amantadine* can be used.

Treatment through the Progression of Parkinson Disease

Two of the *more common* motor complications are the **wearing-off** effect and the **on-off** effect.

The wearing-off effect is most *predictable*, occurring in the *latter part* of the *dosing interval* after a period of relief. Because levodopa is a short-acting agent with an elimination half-life of about 1.5 hours, much of the effect from the evening dose will dissipate by morning.

Treatment through the Progression of Parkinson Disease



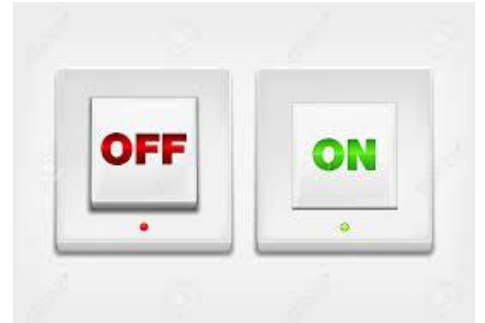
Treatment through the Progression of Parkinson Disease

Wearing off can be **improved** by various means such as *shortening the dosing interval* or with the *addition of adjunctive* therapy (if not already present) with a dopamine agonist, MAO-B inhibitor or levodopa extender such as a COMT inhibitor.

Treatment through the Progression of Parkinson Disease

The **on-off** effect is described as *random fluctuations* from mobility (often associated with dyskinesias) to the parkinsonian state, which appear suddenly as if a *switch has been turned on or off*.

These fluctuations can last *from minutes to hours* and increase in frequency and intensity with time.



Treatment through the Progression of Parkinson Disease

The *pathophysiologic basis* for motor complications and dyskinesias is not entirely clear, but incomplete delivery of dopamine to central receptors is likely responsible.

Because the disease progresses and **dopamine terminals are lost**, the capacity to store dopamine pre-synaptically is diminished, impairing the ability to maintain relatively constant striatal dopamine concentrations.

Treatment through the Progression of Parkinson Disease

Although **off time** should *theoretically* be reduced by the slower rate of plasma levodopa decline, clinical study has generally **not found** a sustained difference in *off-time*, or a reduction in *dyskinesias*, with the CR preparation compared with the immediate release preparation.

(probably because of variable absorption which is 30% less than the IR formulation)



Treatment through the Progression of Parkinson Disease

Patients *converted* from standard carbidopa/levodopa to the CR formulation should receive a dose that will provide **10% more levodopa**, and then the dose should be titrated upward to clinical response.

Treatment through the Progression of Parkinson Disease

Drug	Interaction	Mechanism	Comments
Anticholinergics	↓ Levodopa effect	↓ Gastric emptying, thus ↑ degradation of levodopa in gut, and ↓ amount absorbed	Watch for ↓ levodopa effect when anticholinergics cause ↓ GI motility. When anticholinergic therapy is discontinued in a patient on levodopa, watch for signs of levodopa toxicity. Theoretic interaction with minor clinical significance
Ferrous sulfate	↓ Levodopa oral absorption by 50%	Formation of chelation complex	Avoid concomitant administration or separate administration by at least 2 hours.
Food	↓ Levodopa effect	Large, neutral amino acids compete with levodopa for intestinal absorption	Although levodopa is usually taken with meals to slow absorption and ↓ central emetic effect, high-protein diets should be avoided.
MAOI (eg, phenelzine, tranylcypromine)	Hypertensive crisis	Peripheral dopamine and norepinephrine	Avoid combination use; monoamine oxidase type B (MAO-B) inhibitors such as selegiline can be used, but the dose of levodopa should be reduced after 2–3 days of therapy; carbidopa might minimize hypertensive reaction to levodopa in patients receiving an MAOI.

Treatment through the Progression of Parkinson Disease

Drug	Interaction	Mechanism	Comments
Methyldopa	↑ or ↓ levodopa effect	Acts as central and peripheral decarboxylase inhibitor	Observe for response; may need to switch to another antihypertensive.
Metoclopramide	↓ Levodopa effect	Central dopamine blockade	Avoid combination use.
Neuroleptics (eg, butyrophenones, phenothiazines)	↓ Levodopa effect	Central blockade of dopamine neurotransmission	Avoid combination use; important interaction.
Phenytoin	↓ Levodopa effect	Mechanism unknown	Avoid combination use.
Pyridoxine (vitamin B ₆)	↓ Levodopa effect	Peripheral decarboxylation of levodopa	Not observed when levodopa given with carbidopa; avoid levodopa monotherapy with vitamin B ₆ supplementation.
Tricyclic antidepressants	↓ Levodopa effect	Levodopa degradation in gut because of delayed emptying	Use with caution.

Treatment through the Progression of Parkinson Disease

Amantadine

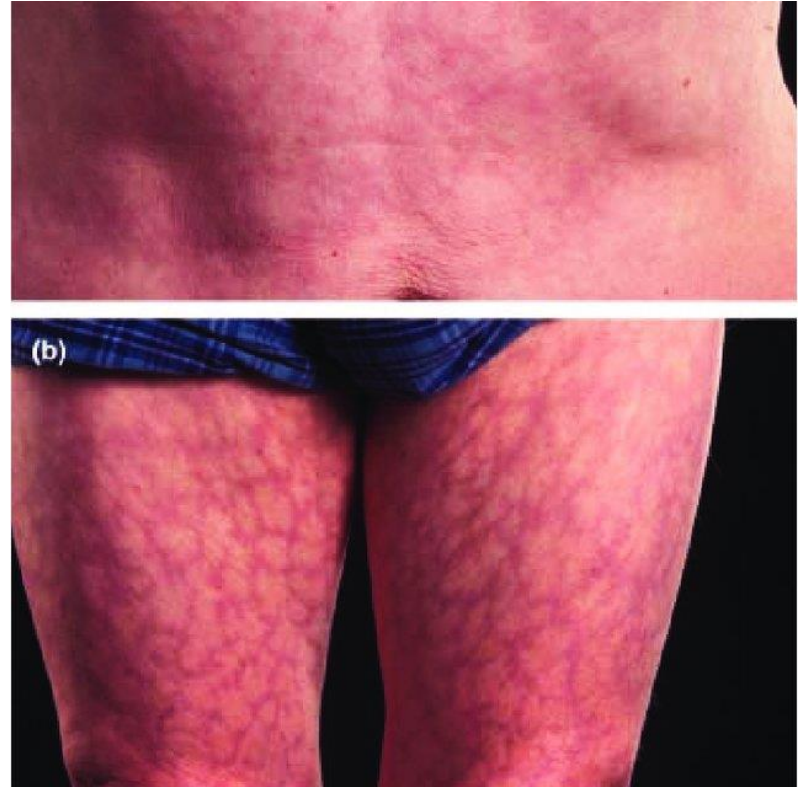
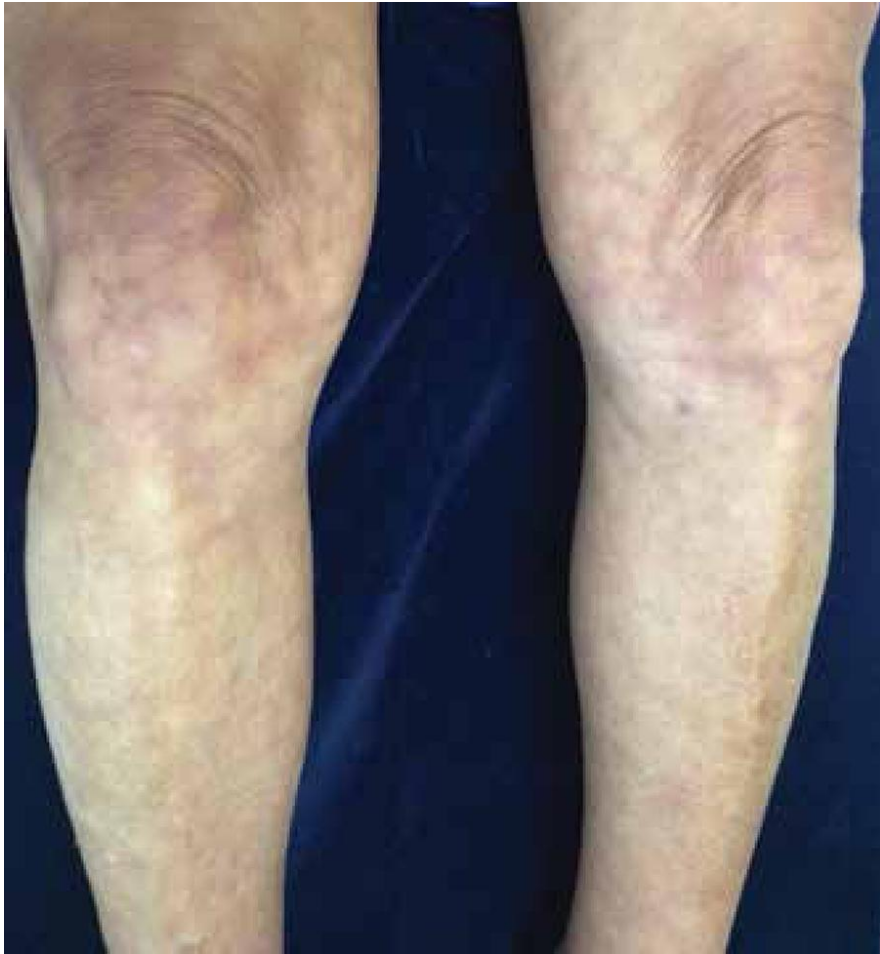
Amantadine **reduces all the symptoms** of parkinsonian disability in about 50% of patients, usually *within days* after starting therapy; however, early trials indicated that amantadine efficacy might be limited by the development of **tachyphylaxis** within 1 to 3 months.



Treatment through the Progression of Parkinson Disease

Livedo reticularis, a rose-colored mottling of the skin usually involving the lower extremities, can occur with amantadine as early as 2 weeks after initiating therapy. The consequences of livedo reticularis are entirely **cosmetic**, and discontinuation of therapy is unnecessary.

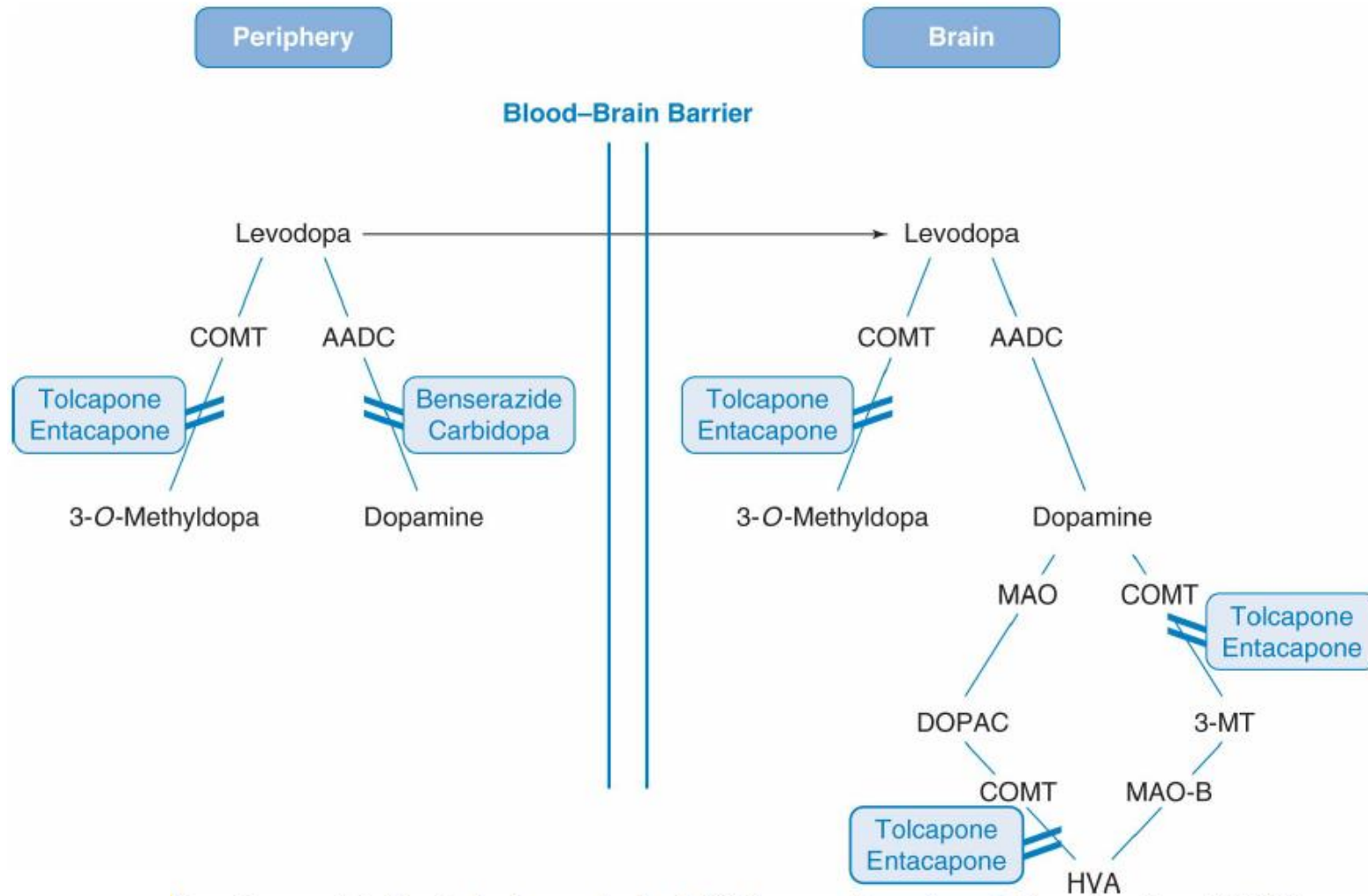
Ankle edema may be seen in association with livedo reticularis. Elevation of the legs, diuretic therapy, and dosage reduction often alleviate the edema.



Treatment through the Progression of Parkinson Disease

Catechol-o-methyltransferase Inhibitors

When carbidopa, an inhibitor of aromatic AAD, is co-administered with levodopa, the peripheral conversion of levodopa to dopamine via this pathway is inhibited; as a consequence, the conversion of levodopa to 3-O-methyldopa (3-OMD) by **COMT** is **amplified** and *becomes the major metabolic pathway* for levodopa degradation.



Levodopa metabolism in the human body. AADC, aromatic amino acid decarboxylase; COMT, catechol-O-methyltransferase; DOPAC, 3,4-dihydroxyphenylacetic acid; MAO, monoamine oxidase; 3-MT, 3-methoxytyramine.

Treatment through the Progression of Parkinson Disease

Use of these agents is associated with *increased on-time* and a decrease in the daily levodopa dose.

Because of the risks for hepatotoxicity associated with tolcapone, **entacapone** is the preferred **COMT** inhibitor.

Treatment through the Progression of Parkinson Disease

Dosing

Entacapone is approved for use as *adjunctive therapy* to levodopa for the treatment of PD in patients experiencing **wearing-off** or **end-of-dose deterioration**.

It is given as one 200-mg tablet with each carbidopa/levodopa administration, **up to eight** tablets/day.

It is available in a combination tablet with a 1:4 ratio of immediate-release carbidopa/levodopa that patients can be switched to once they are stabilized on individual formulations of carbidopa/levodopa and entacapone.

Treatment through the Progression of Parkinson Disease

Adverse Effects

Most entacapone-induced adverse effects are *consistent* with increased levodopa exposure. They include dyskinesias (50%–60%), dizziness (10%–25%), nausea (15%–20%), and hallucinations (1%–14%).

Reducing the levodopa dosage by 10% to 15% as a strategy for circumventing these effects is successful in about one third of patients experiencing dyskinesias.

Treatment through the Progression of Parkinson Disease

Urine discoloration (brownish orange) is attributed to entacapone and its metabolites and is considered benign, but patients should be counseled regarding this effect.

The most common reason for withdrawal from clinical studies and discontinuation of therapy was severe **diarrhea**.

Investigational Pharmacotherapy

Antioxidants

Antioxidants have been hypothesized to benefit patients with PD through their ability to act as free radical scavengers.

Despite the theoretic benefit, clinical data are **lacking** to support the routine use of α -tocopherol.



Investigational Pharmacotherapy

Coenzyme Q10

Coenzyme Q10 (CoQ10) is an antioxidant involved in the mitochondrial electron transport chain and has been shown to be *reduced in patients with PD*. Due to the lack of data supporting CoQ10, its use should be **avoided**.



Investigational Pharmacotherapy

Creatine and minocycline

Minocycline (anti-inflammatory and antiapoptotic properties) and creatine (an antioxidant and enhances mitochondrial energy production) were evaluated to determine both safety and if either slowed the progressive decline in function associated with PD.

None were effective in clinical trials.

Investigational Pharmacotherapy

Vitamins

Vitamins may play a role as antioxidants and affect biologic functions by regulating gene expression, which may be beneficial for the treatment of PD. **Vitamins D** and **B12** may hold some promise in PD.