

Treatment of Neurodegenerative Diseases

Dr. Omar Shaheen



- Most drugs that affect the central nervous system (CNS) act by altering some step in the neurotransmission process
- This chapter provides an overview of the CNS, with a focus on those neurotransmitters that are involved in the actions of the clinically useful CNS drugs.
- Neurodegenerative disorders are CNS disorders that respond to drug therapy:
 - Parkinson disease
 - Alzheimer disease
 - Multiple sclerosis (MS)
 - Amyotrophic lateral sclerosis (ALS)



ANTI-PARKINSON DRUGS

Amantadine GOCOVRI

Apomorphine APOKYN

Benzotropine COGENTIN

Bromocriptine PARLODEL

Carbidopa LODOSYN

Entacapone COMTAN

Levodopa (w/ Carbidopa) SINEMET

Levodopa (w/ Carbidopa+

Entacapone) STALEVO

Pramipexole MIRAPEX

Rasagiline AZILECT

Ropinirole REQUIP

Rotigotine NEUPRO

Safinamide XADAGO

Selegiline (Deprenyl) ELDEPRYL, ZELAPAR

Tolcapone TASMAR

Trihexyphenidyl GENERIC ONLY



ANTI-ALZHEIMER DRUGS

Donepezil ARICEPT

Galantamine RAZADYNE

Memantine NAMENDA

Rivastigmine EXELON

ANTI-MULTIPLE SCLEROSIS DRUGS

Alemtuzumab LEMTRADA

Azathioprine AZASAN, IMURAN

Cyclophosphamide GENERIC ONLY

Daclizumab ZINBRYTA

Dalfampridine AMPYRA

Dexamethasone DECADRON

Dimethyl fumarate TECFIDERA

Fingolimod GILENYA

Glatiramer COPAXONE

Interferon β_{1a} AVONEX, REBIF

Interferon β_{1b} BETASERON, EXTAVIA

Natalizumab TYSABRI

Ocrelizumab OCREVUS

Prednisone DELTASONE

Teriflunomide AUBAGIO

ANTI-ALS DRUGS

Edaravone RADICAVA

Riluzole RILUTEK



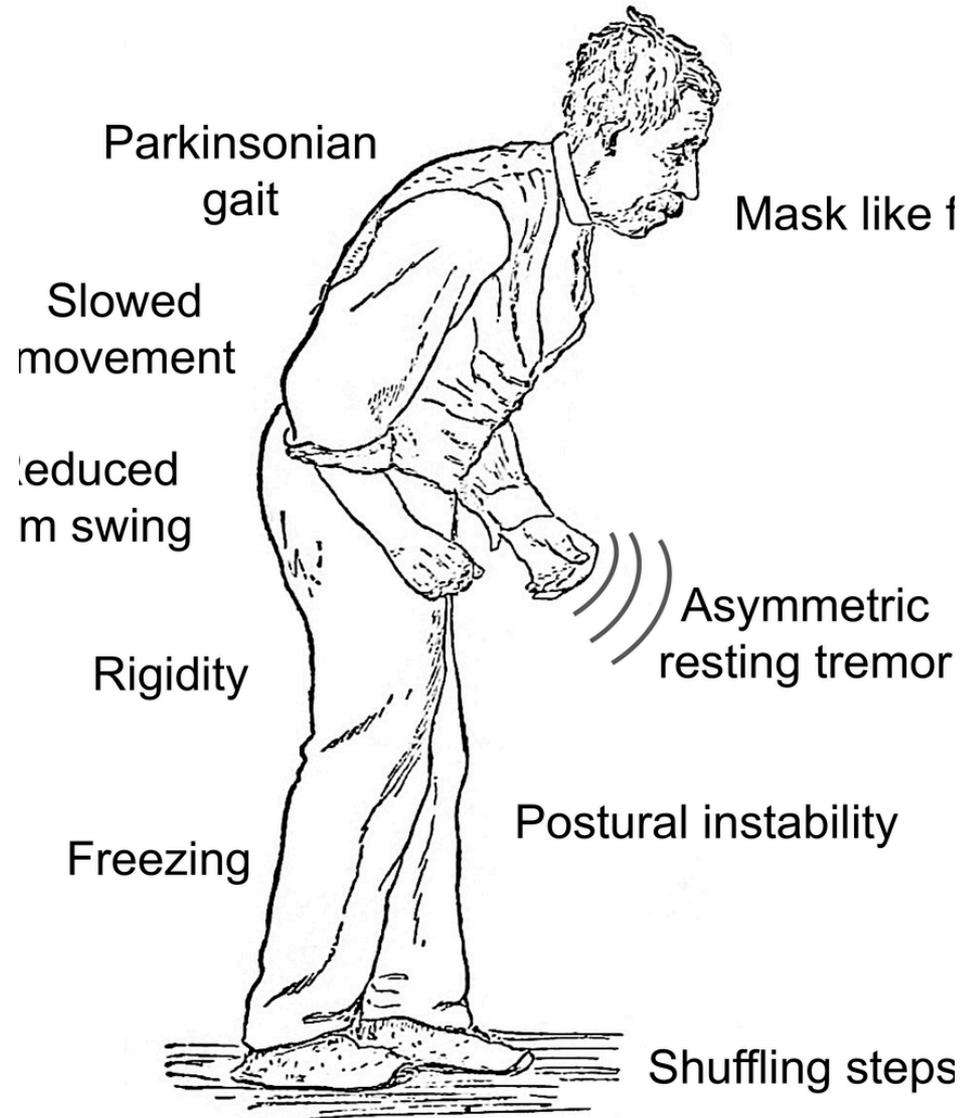
Parkinson disease

- Parkinson disease is a chronic, progressive, age-related neurodegenerative disease resulting from the loss of dopamine-containing neurons in the substantia nigra.
- The basal ganglia are made up of the corpus striatum (which is composed of the caudate nucleus and putamen), globus pallidus, subthalamic nucleus, and substantia nigra. It functions to control movement in conjunction with the cerebellum and motor cortex



Parkinson disease

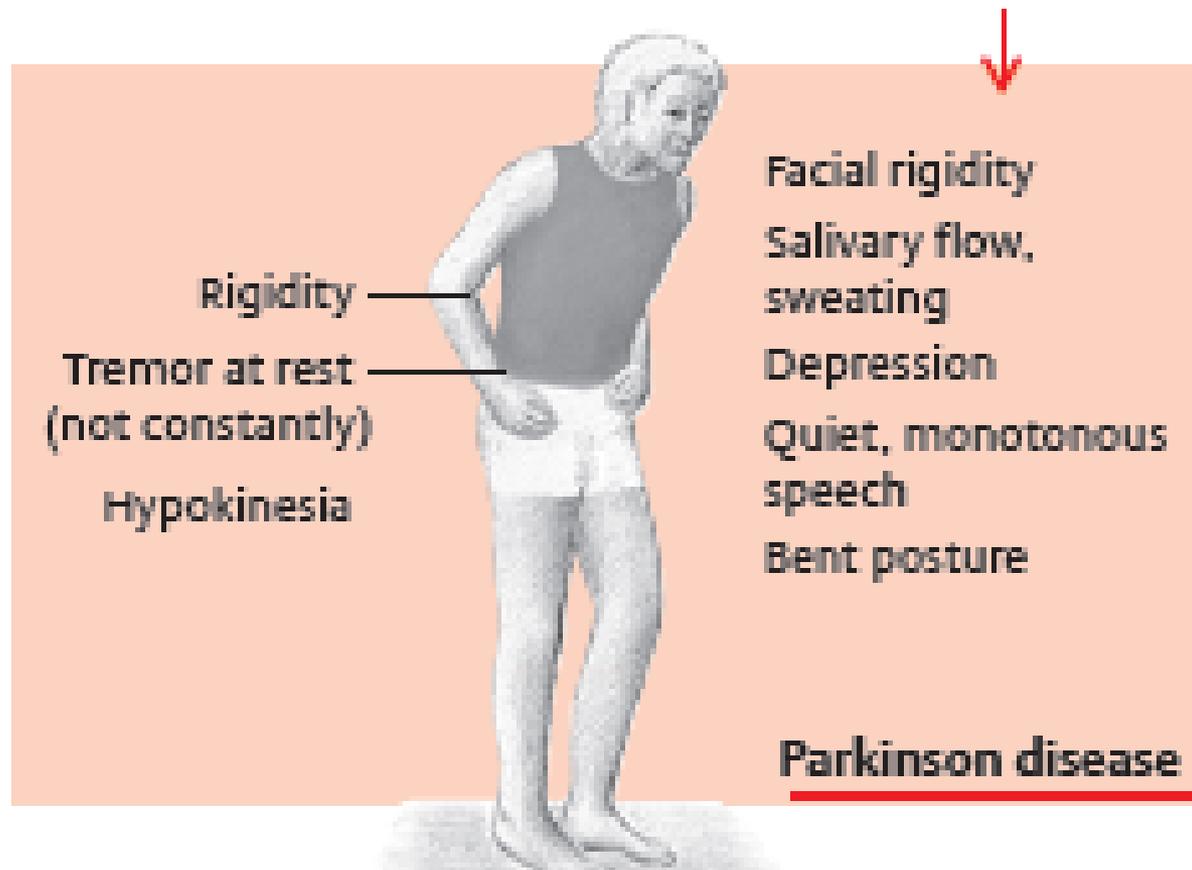
- Symptoms usually start between 60 and 70 years of age and include a :
 - “pill-rolling” tremor
 - Rigidity (limbs resist extension throughout movement),
 - Bradykinesia (slow execution of movement and speech), resulting in a masklike face and shuffling gait.



Signs and symptoms of Parkinson disease

- Inhibition of the thalamus suppresses voluntary movement and accounts for the signs and symptoms of Parkinson disease including
 - — Pill-rolling tremor that is present at rest and that increases with stress
 - — Bradykinesia (slow initiation of movements) and decrease of spontaneous movements
 - — Masked faces
 - — Increased muscle tone and cogwheel rigidity
 - — Postural disturbances occurring in later phases. (The patient adopts a stooped position and a festinating gait.)
 - — Lewy body dementia (LBD) in one third of patients

Signs and symptoms of Parkinson disease



Parkinson disease (treatments)

- There are many drug treatment options for Parkinson disease.
- Levodopa is a dopamine precursor that is converted to dopamine in the brain by dopa decarboxylase.
- Levodopa is often used in combination with carbidopa, a drug that prevents the peripheral conversion of levodopa to dopamine by inhibiting dopa decarboxylase.
- Dopamine agonists (e.g., bromocriptine) mimic the effects of dopamine in the brain.
- Catechol-*O*-methyltransferase (COMT) inhibitors (e.g., entacapone) are used to prevent the peripheral breakdown of levodopa.
- Monoamine oxidase B (MAO-B) inhibitors (e.g., selegiline) prevent the breakdown of dopamine in the brain. Anticholinergic drugs (e.g., benztropine) may be given as an adjunct for the tremor



Nigrostriatal Tract and Parkinson Disease

- In a normal, healthy person, there is a balance between inhibitory dopamine components and excitatory acetylcholine components in the nigrostriatal tract.
- In Parkinson disease, however, there is a deficiency of the dopamine component; therefore, the goal of therapy is to restore dopamine levels. Alternatively, the acetylcholine component should be decreased



Antiparkinsonian Drugs

- Dopamine cannot be given directly because it is rapidly metabolized in the periphery, has adverse side effects on the cardiovascular system, and very little penetrates the CNS.



Strategies to combat the dopamine deficiency include:

- Increasing dopamine precursor levels (levodopa),
- Decreasing dopamine breakdown (entacapone, tolcapone, selegiline, and rasagiline)
- Enhancing dopamine release (amantadine)
- And administering dopamine receptor agonists (bromocriptine, pramipexole, and ropinirole).



Levodopa

- Mechanism of action. Levodopa, or l-3,4-dihydroxyphenylalanine (l-dopa), is a precursor
- in dopamine synthesis. It is formed from L-tyrosine and is transformed to dopamine by aromatic
- l-amino acid decarboxylase (dopa decarboxylase). Levodopa itself is pharmacologically inert; its effects are a result of decarboxylation to dopamine.



Pharmacokinetics

- — Levodopa is rapidly absorbed from the intestine by active transport.
- — Administration with meals reduces absorption.
- — It has a short plasma half-life of 1 to 3 hours.
- — It undergoes peripheral decarboxylation.
- — Small amounts enter the central nervous system (CNS).
- — It is converted to dihydroxyphenylacetic acid and homovanillic acid and excreted in the urine.



The effects of levodopa.

Table 14.1 ► Effects of Levodopa

System	Effects
CNS	Relieves bradykinesia and rigidity preferentially over relieving tremor Secondary improvements are seen in posture, gait, ability to modify facial expression, speech, and handwriting. There is no relief of dementia.
Cardiovascular system	Postural (orthostatic) hypotension and cardiac stimulation occur, although tolerance usually develops (mechanism unknown).
Endocrine system	Prolactin secretion is inhibited. ^a Growth hormone release may also be observed in healthy individuals but not in patients with Parkinson disease.

^a Dopamine is a prolactin-inhibiting hormone.

Abbreviation: CNS, central nervous system.



Side effects experienced by most patients who take levodopa.

Table 14.2 ▶ Side Effects of Levodopa^a

Side Effects	
Short-term	Nausea and vomiting Cardiac arrhythmias
Long-term	Abnormal movements such as tics, grimacing, head bobbing, and oscillatory movements of the limbs are seen in 50% of patients within 2 to 4 months and in 80% of patients by 1 year. No tolerance develops to these effects, and they will worsen if the dose is not reduced. Psychiatric disturbances (serious in 15% of patients): hallucinations, paranoia, mania, insomnia, anxiety, nightmares, and depression False-positive test for ketoacidosis by the dipstick test due to the presence of levodopa metabolites Red-colored urine that changes to black on exposure to air or alkali

^a All side effects are seen in the majority of patients. These are reversible and can be controlled by reducing the dose.



Drug interactions

- — Pyridoxine, a form of vitamin B6 found in multivitamins, is a cofactor for dopa decarboxylase and may enhance the metabolism of levodopa.
- — Antipsychotics antagonize dopamine receptors and are thus contraindicated with levodopa.
- — Reserpine is contraindicated because it depletes dopamine.
- — Monoamine oxidase inhibitors (MAOIs) block dopamine breakdown and may exaggerate effects (hypertensive crisis and hyperpyrexia). MAOIs should be withdrawn at least 2 weeks prior to levodopa administration.
- — Anticholinergics may slow gastric emptying.
- Contraindications. Care must be exercised in patients with heart disease, cerebrovascular
- disease, or neurological disease.



Aromatic L-Amino Acid Decarboxylase Inhibitors: Carbidopa and Benserazide

- Carbidopa is the only type available in the United States. Benserazide, which is available in Europe and Canada, has similar properties.
- Mechanism of action. These agents inhibit the peripheral production of dopamine from levodopa by inhibiting dopa decarboxylase. This allows more levodopa to be available to the CNS .



Uses. Carbidopa and benserazide are usually administered with levodopa. They confer the following advantages:

- They allow for a dose reduction of levodopa and for a reduced number of doses.
- The effective dose is achieved more rapidly.
- A larger percentage of patients responds favorably.
- Pyridoxine interaction is avoided.
- **Side effects.** No side effects are seen when these agents are given alone. All side effects are associated with the increased effect of levodopa.
 - — CNS side effects may appear more frequently or earlier in therapy.
 - — There are fewer peripheral side effects, such as nausea, vomiting, and cardiac effects.



Entacapone and Tolcapone

- Mechanism of action. Entacapone and tolcapone are selective and reversible inhibitors of catechol-*O*-methyltransferase (COMT), which is the enzyme responsible for the peripheral breakdown of levodopa. This allows more levodopa to be available in the CNS .
- They act mainly in the periphery.
- Uses. These agents are given as adjunctive therapy to patients experiencing fluctuations in
- disability related to levodopa and dopa-decarboxylase inhibitor combinations).



Entacapone and Tolcapone

- Side effects. These agents do not cause any adverse effects alone, but they enhance the adverse effects of levodopa.
- — Acute liver failure may occur with tolcapone.
- Drug interactions. These agents may potentiate the actions of drugs metabolized by COMT (i.e., dopamine, epinephrine, and methyldopa).



Amantadine

- Mechanism of action. Amantadine probably enhances dopamine release in the CNS.
- Uses
- Used in early stages of parkinsonism or as a supplement to levodopa.
- Side effects
- Neurologic: restlessness, irritability, insomnia, and headache at lower doses, progressing to
- agitation and delirium at higher doses
- Gastrointestinal: nausea and diarrhea



Bromocriptine, Pramipexole, and Ropinirole

- Mechanism of action. These agents are dopamine agonists.
- Uses
 - — Parkinson disease
 - — Restless leg syndrome (pramipexole and ropinirole)
- Side effects
 - — The same as levodopa



Selegiline and Rasagiline

- Mechanism of action. Selegiline and rasagiline are selective inhibitors of MAO-B, the enzyme involved in dopamine metabolism in the CNS .
- Side effects. These agents potentiate the effects of dopamine in the brain but do not potentiate
- The effects of catecholamines to produce a hypertensive crisis.
- Trihexyphenidyl, Benztropine, Procyclidine, and Diphenhydramine
- These anticholinergics were the primary agents prior to the introduction of levodopa.



Selegiline and Rasagiline

- Uses
 - — Useful in early stages, in patients who are intolerant to levodopa, or as a supplement to
 - levodopa therapy
 - — More effective in relieving tremor than either rigidity or bradykinesia
- Side effects
 - — Cycloplegia, constipation, and urinary retention
 - — CNS: confusion, delirium, and hallucinations
 - — Paralysis of the ciliary muscle of the eye



The End
Have a nice day

