Treatment Parkinson
Parkinsonism

• Parkinsonism is a progressive neurological disorder of muscle movement, characterized by:

✓ Tremors, muscular rigidity, bradykinesia (slowness in initiating and carrying out voluntary movements), and postural and gait abnormalities.

✓ Most cases involve people over the age of 65, among whom the incidence is about 1 in 100 individuals.
Etiology

- The cause of Parkinson’s disease is unknown for most patients.
- The disease is correlated with destruction of dopaminergic neurons in the substantia nigra with a consequent reduction of dopamine actions in the corpus striatum, parts of the basal ganglia system that are involved in motor control.
- In Parkinson’s disease, destruction of cells in the substantia nigra results in the degeneration of the nerve terminals that secrete dopamine in the neostriatum.
- The normal inhibitory influence of dopamine on cholinergic neurons in the neostriatum is significantly diminished, resulting in overproduction or a relative overactivity of acetylcholine by the stimulatory neurons.
- This triggers a chain of abnormal signaling, resulting in loss of the control of muscle movements.
• Secondary parkinsonism: Drugs such as the phenothiazines and haloperidol, whose major pharmacologic action is blockade of dopamine receptors in the brain, may produce parkinsonian symptoms (also called pseudoparkinsonism).

• These drugs should be used with caution in patients with Parkinson’s disease.
Strategy of treatment

- In addition to an abundance of inhibitory dopaminergic neurons, the neostriatum is also rich in excitatory cholinergic neurons that oppose the action of dopamine.
- Many of the symptoms of parkinsonism reflect an imbalance between the excitatory cholinergic neurons and the greatly diminished number of inhibitory dopaminergic neurons.

✓ Therapy is aimed at restoring dopamine in the basal ganglia and antagonizing the excitatory effect of cholinergic neurons, thus reestablishing the correct dopamine/acetylcholine balance.
DRUGS USED IN PARKINSON’S DISEASE

• Many currently available drugs aim to maintain CNS dopamine levels as constant as possible.
• These agents offer temporary relief from the symptoms of the disorder, but they do not arrest or reverse the neuronal degeneration caused by the disease.

A. Levodopa and carbidopa

• **Levodopa** [lee-voe-DOE-pa] *is a metabolic precursor of dopamine.*
• It restores dopaminergic neurotransmission in the neostriatum by enhancing the synthesis of dopamine in the surviving neurons of the substantia nigra.
• In early disease, the number of residual dopaminergic neurons in the substantia nigra (typically about 20% of normal) is adequate for conversion of *levodopa to dopamine.*
• In new patients, the therapeutic response to *levodopa is consistent,* and the patient rarely complains that the drug effects “wear off.”
• Unfortunately, with time, the number of neurons decreases, and fewer cells are capable of converting exogenously administered levodopa to dopamine.

• Consequently, motor control fluctuation develops.

• Relief provided by levodopa is only symptomatic, and it lasts only while the drug is present in the body.

• The effects of levodopa on the CNS can be greatly enhanced by coadministering carbidopa [kar-bi-DOE-pa], a dopamine decarboxylase inhibitor that does not cross the blood–brain barrier.
Mechanism of action:
a. Levodopa: Dopamine does not cross the blood–brain barrier, but its immediate precursor, levodopa, is actively transported into the CNS and converted to dopamine.

- **Levodopa** must be administered with carbidopa. Without **carbidopa**, much of the drug is decarboxylated to dopamine in the periphery, resulting in nausea, vomiting, cardiac arrhythmias, and hypotension.
Figure 8.5
Synthesis of dopamine from levodopa in the absence and presence of carbidopa, an inhibitor of dopamine decarboxylase in the peripheral tissues. GI = gastrointestinal.
Carbidopa: Carbidopa, a dopamine decarboxylase inhibitor, diminishes the metabolism of levodopa in the periphery, thereby increasing the availability of levodopa to the CNS.

The addition of carbidopa lowers the dose of levodopa needed by four- to fivefold and, consequently, decreases the severity of the side effects arising from peripherally formed dopamine.

2. **Therapeutic uses:** **Levodopa in combination with carbidopa is an efficacious drug regimen for the treatment of Parkinson’s disease.**

- It decreases rigidity, tremors, and other symptoms of parkinsonism. In approximately two-thirds of patients with Parkinson’s disease,
- levodopa–carbidopa substantially reduces the severity of symptoms for the first few years of treatment.
- Patients typically experience a decline in response during the 3rd to 5th year of therapy.
- Withdrawal from the drug must be gradual.
• Absorption and metabolism: The drug is absorbed rapidly from the small intestine (when empty of food).

• Levodopa has an extremely short half-life (1 to 2 hours), which causes fluctuations in plasma concentration.

• This may produce fluctuations in motor response, which generally correlate with the plasma concentration of levodopa, or perhaps give rise to the more troublesome “on–off” phenomenon, in which the motor fluctuations are not related to plasma levels in a simple way.
• Motor fluctuations may cause the patient to suddenly lose normal mobility and experience tremors, cramps, and immobility.

• Ingestion of meals, particularly if high in protein, interferes with the transport of levodopa into the CNS.

• Thus, levodopa should be taken on an empty stomach, typically 30 minutes before a meal.
Adverse effects:

a. Peripheral effects: Anorexia, nausea, and vomiting occur because of stimulation of the chemoreceptor trigger zone

- Tachycardia and ventricular extrasystoles result from dopaminergic action on the heart. Hypotension may also develop.

- Adrenergic action on the iris causes mydriasis.

- Saliva and urine are a brownish color because of the melanin pigment produced from catecholamine oxidation.
b. CNS effects: Visual and auditory hallucinations and abnormal involuntary movements (dyskinesias) may occur.

• These effects are the opposite of parkinsonian symptoms and reflect overactivity of dopamine in the basal ganglia.

• *Levodopa can also* cause mood changes, depression, psychosis, and anxiety.
**Interactions:**

- **The vitamin pyridoxine (B6) increases the peripheral breakdown of levodopa and diminishes its effectiveness.**
- Concomitant administration of *levodopa and non-selective monoamine* oxidase inhibitors (MAOIs), such as *phenelzine, can produce* a hypertensive crisis caused by enhanced catecholamine production. Therefore, concomitant administration of these agents is contraindicated.
- In many psychotic patients, *levodopa exacerbates symptoms,* possibly through the buildup of central catecholamines.
- **Cardiac patients** should be carefully monitored for the possible development of arrhythmias.
- **Antipsychotic drugs are generally contraindicated in Parkinson’s disease,** because they potently block dopamine receptors and may augment parkinsonian symptoms.
- However, **low doses of atypical antipsychotics are sometimes used to treat levodopa-induced psychotic symptoms.**
Diminished effect due to increased peripheral metabolism

Pyridoxine

Levodopa

MAO inhibitors

Hypertensive crisis due to increased catecholamines

Figure 8.7
Some drug interactions observed with levodopa. MAO = monoamine oxidase.
Selegiline and rasagiline

- **Selegiline** [seh-LEDGE-ah-leen], also called **deprenyl** [DE-pre-nill], selectively inhibits monoamine oxidase (MAO) type B (metabolizes dopamine) at low to moderate doses.
- It does not inhibit MAO type A (metabolizes norepinephrine and serotonin) unless given above recommended doses, where it loses its selectivity.
  - By decreasing the metabolism of dopamine, *selegiline increases dopamine levels in the brain.*
- When *selegiline is administered with levodopa*, it enhances the actions of *levodopa and substantially reduces the required dose.*
- Unlike nonselective MAOIs, *selegiline at recommended doses has little potential for causing hypertensive crises.*
- The drug loses selectivity at high doses, and there is a risk for severe hypertension.
- **Selegiline** is metabolized to *methamphetamine and amphetamine*, whose stimulating properties may produce *insomnia* if the drug is administered later than mid-afternoon.
Figure 8.8

Action of selegiline (deprenyl) in dopamine metabolism. MAO B = monoamine oxidase type B.
Rasagiline

• Rasagiline[ra-SAgi-leen], an irreversible and selective inhibitor of brain MAO type B, has five times the potency of selegiline.

• Unlike selegiline, rasagiline is not metabolized to an amphetamine-like substance.
C. Catechol-O-methyltransferase inhibitors

• Normally, the methylation of levodopa by catechol-O-methyltransferase (COMT) to 3-O-methyldopa is a minor pathway for levodopa metabolism.

• However, when peripheral dopamine decarboxylase activity is inhibited by carbidopa, a significant concentration of 3-O-methyldopa is formed that competes with levodopa for active transport into the CNS.

✓ Entacapone [en-TAK-a-ponce] and
✓ Tolcapone [TOLE-ka-ponce] selectively and reversibly inhibit COMT.

• Inhibition of COMT by these agents leads to decreased plasma concentrations of 3-O-methyldopa, increased central uptake of levodopa, and greater concentrations of brain dopamine.

• Both of these agents reduce the symptoms of “wearing-off” phenomena seen in patients on levodopa–carbidopa.

• The two drugs differ primarily in their pharmacokinetic and adverse effect profiles.
Figure 8.9
Effect of entacapone on dopa concentration in the central nervous system (CNS). COMT = catechol-O-methyltransferase.
Pharmacokinetics:

• Oral absorption of both drugs occurs readily and is not influenced by food.

• **Tolcapone** has a relatively long duration of action (probably due to its affinity for the enzyme) compared to **entacapone**, which requires more frequent dosing.

• Both drugs are extensively metabolized and eliminated in feces and urine.

• The dosage may need to be adjusted in patients with moderate or severe cirrhosis.
**Adverse effects:**

- **Both drugs exhibit** adverse effects that are observed in patients taking *levodopa–carbidopa*, *including diarrhea*, postural hypotension, nausea, anorexia, dyskinesias, hallucinations, and sleep disorders.
- Most seriously, fulminating hepatic necrosis is associated with *tolcapone use*.
- *Therefore, it should be* used, along with appropriate hepatic function monitoring, only in patients in whom other modalities have failed.
- **Entacapone** does not exhibit this toxicity and has largely replaced *tolcapone*. 
D. Dopamine receptor agonists

- This group of antiparkinsonian compounds includes
  - Ergot derivative: **Bromocriptine**.
  - Nonergot drugs:
    - **Ropinirole** [roe-PIN-i-role]
    - **Pramipexole** [pra-mi-PEX-ole]
    - **Rotigotine** [ro-TIG-oh-teen], and the newer agent,
    - **Apomorphine** [A-poe-more-feen].

- **These agents have a longer duration of action than that of levodopa and are effective in** patients exhibiting fluctuations in response to levodopa.

- **Initial therapy** with these drugs is associated with less risk of developing dyskinesias and motor fluctuations as compared to patients started on levodopa.
• Bromocriptine, pramipexole, and ropinirole are effective in patients with Parkinson’s disease complicated by motor fluctuations and dyskinesias.
• However, these drugs are ineffective in patients who have not responded to levodopa.
• Apomorphine is an injectable dopamine agonist that is used in severe and advanced stages of the disease to supplement oral medications.
• Side effects severely limit the utility of the dopamine agonists.
Dopamine agonists delay motor complications and are most commonly initiated before levodopa in patients who have mild disease and a younger age of onset because they may delay the need to start levodopa therapy.

Figure 8.11
Motor complications in patients treated with levodopa or dopamine agonists.
Bromocriptine:

- The actions of the ergot derivative **bromocriptine** broe-moe-KRIP-teen] are similar to those of **levodopa**, except that hallucinations, confusion, delirium, nausea, and orthostatic hypotension are more common, whereas dyskinesia is less prominent.

- In **psychiatric illness**, **bromocriptine may cause the mental condition to worsen**.

- It should be used with caution in patients with a history of myocardial infarction or peripheral vascular disease.

- Because **bromocriptine is an ergot derivative**, it has the **potential** to cause pulmonary and retroperitoneal fibrosis.
Apomorphine, pramipexole, ropinirole, and rotigotine:

- These are nonergot dopamine agonists that are approved for the treatment of Parkinson’s disease.
- Pramipexole and ropinirole are orally active agents.
- Apomorphine and rotigotine are available in injectable and transdermal delivery systems, respectively.
- Apomorphine is used for acute management of the hypomobility “off” phenomenon in advanced Parkinson’s disease.
- Rotigotine is administered as a once-daily transdermal patch that provides even drug levels over 24 hours.
- These agents alleviate the motor deficits in patients who have never taken levodopa and also in patients with advanced Parkinson’s disease who are treated with levodopa.
- Dopamine agonists may delay the need to use levodopa in early Parkinson’s disease and may decrease the dose of levodopa in advanced Parkinson’s disease.
Unlike the ergotamine derivatives, these agents do not exacerbate peripheral vascular disorders or cause fibrosis.

Nausea, hallucinations, insomnia, dizziness, constipation, and orthostatic hypotension are among the more distressing side effects of these drugs.

but dyskinesias are less frequent than with levodopa.

Pramipexole is mainly excreted unchanged in the urine, and dosage adjustments are needed in renal dysfunction.

Cimetidine inhibits renal tubular secretion of organic bases and may significantly increase the half-life of pramipexole.

The fluoroquinolone antibiotics and other inhibitors of the cytochrome P450 (CYP450) 1A2 isoenzyme (for example, fluoxetine) may inhibit the metabolism of ropinirole, requiring an adjustment in ropinirole dosage.
E. Amantadine

- It was accidentally discovered that the **antiviral drug amantadine** [a-MAN-ta-deen], used to treat influenza, has an antiparkinsonian action.
- Amantadine has several effects on a number of neurotransmitters implicated in parkinsonism:
  - Increasing the release of dopamine.
  - Blocking cholinergic receptors.
  - Inhibiting the N-methyl D-aspartate (NMDA) type of glutamate receptors.
  - Current evidence supports action at NMDA receptors as the primary action at therapeutic concentrations.

  **[Note: If dopamine release is already at a maximum, amantadine has no effect.]**

- The drug may cause restlessness, agitation, confusion, and hallucinations, and, at high doses, it may induce acute toxic psychosis.
- Orthostatic hypotension, urinary retention, peripheral edema, and dry mouth also may occur.
- **Amantadine is less efficacious than levodopa,** and **tolerance** develops more readily.
- Amantadine has fewer side effects.
F. Antimuscarinic agents

- The antimuscarinic agents are much **less efficacious than levodopa** and play only an adjuvant role in antiparkinsonism therapy.
- The actions of **benztropine** [BENZ-troe-peen], **trihexyphenidyl** [tri-hex-ee-FENi-dill], **procyclidine** [pro-SYE-kli-deen], and **biperiden** [bi-PER-i-den] are similar, although individual patients may respond more favorably to one drug.
- Blockage of cholinergic transmission produces effects similar to augmentation of dopaminergic transmission, since it helps to correct the imbalance in the dopamine/acetylcholine ratio.
- These agents can induce mood changes and produce xerostomia (dryness of the mouth), constipation, and visual problems typical of muscarinic blockers.
- They interfere with gastrointestinal peristalsis and are contraindicated in patients with glaucoma, prostatic hyperplasia, or pyloric stenosis.