PHARMACOLOGY

Drugs for Parkinson's Disease

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DISCLOSURE

None

Use Statement

OBJECTIVES

1. Identify the appropriate drugs and drug classes for managing Parkinson's disease
2. Explain the mechanism of action of dopamine precursors/decarboxylase inhibitors, dopamine agonists, catechol-O-methyl transferase (COMT) inhibitors, monoamine oxidase-B (MAO-B) inhibitors, and anticholinergics and relate each to the underlying pathophysiology of Parkinson's disease
3. Describe adverse effects and contraindications to dopamine precursors/decarboxylase inhibitors, dopamine agonists, catechol-O-methyl transferase (COMT) inhibitors, monoamine oxidase-B (MAO-B) inhibitors, and anticholinergics
4. Describe the clinically important drug interactions of dopamine precursors/decarboxylase inhibitors, dopamine agonists, catechol-O-methyl transferase (COMT) inhibitors, monoamine oxidase-B (MAO-B) inhibitors, and anticholinergics

Tolcapone may be of value in patients being treated with levodopa-carbidopa because it

Bradykinesia has made drug treatment necessary in a 60-year-old man with Parkinson disease, and therapy is to be initiated with levodopa. The prescribing physician will (or should) know that levodopa

Concerning the drugs used in parkinsonism, which statement is most accurate?

Dopamine receptor agonists should never be used in Parkinson disease before a trial of levodopa	0%
Levodopa causes mydriasis and may precipitate an acute attack of glaucoma	0%
Selegiline is a selective inhibitor of COMT	0%
The primary benefit of antimuscarinic drugs in parkinsonism is their ability to relieve bradykinesia	0%
Therapeutic effects of amantadine continue for several years	0%

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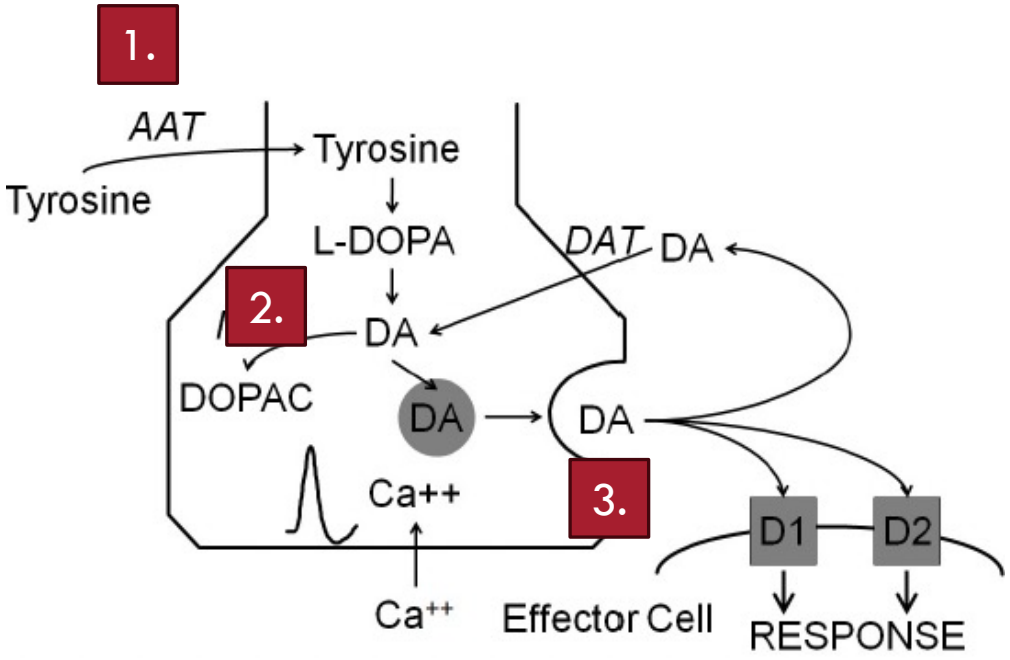
PARKINSON'S DISEASE

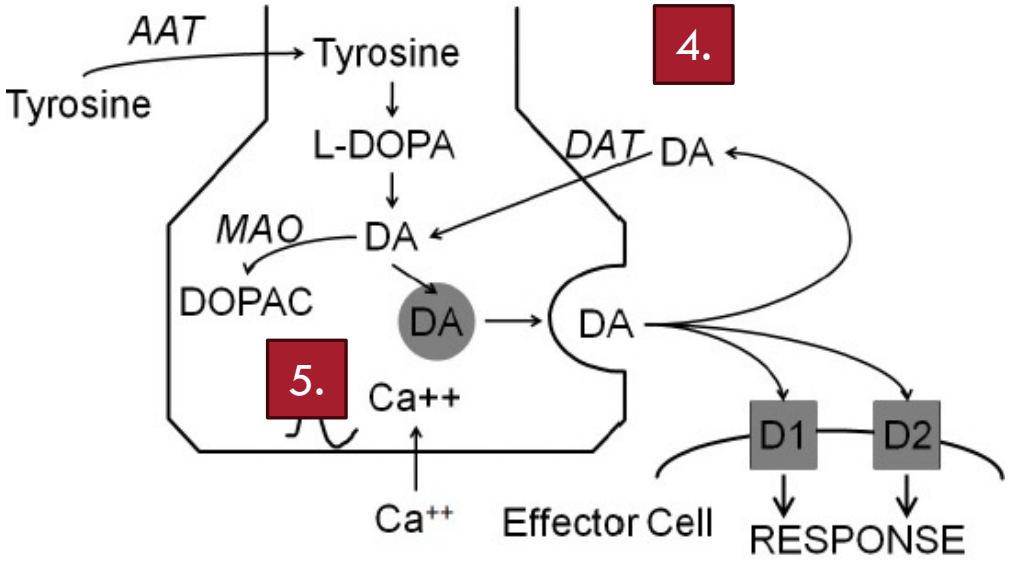
DOPAMINERGIC TERMINAL

1. Catecholamine precursor is tyrosine
   - Taken up by dopaminergic nerves via an amino acid transporter (AAT)
2. Dopamine (DA) synthesized in cytoplasm and transported into secretory vesicles
3. Upon nerve cell stimulation, DA released into the synaptic cleft
   - DA can stimulate postsynaptic DA receptors
   - D1 and D2 receptors important in brain regions involved in Parkinson's disease
   - Stimulation of D2 receptors is largely responsible for reducing rigidity and bradykinesia



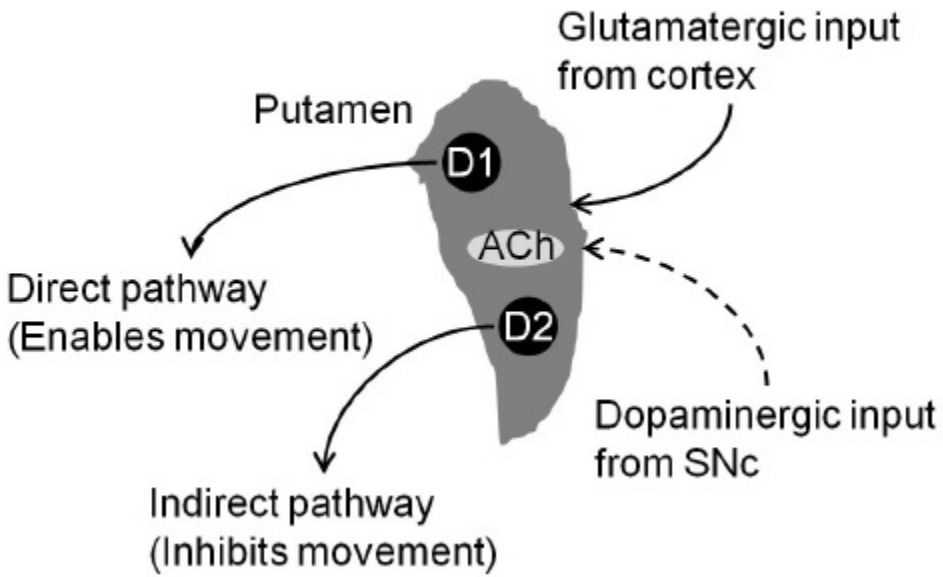
DOPAMINERGIC TERMINAL

4. DA is transported out of the synaptic cleft by the selective, Na+-coupled dopamine transporter (DAT)
5. Cytoplasmic DA is re-transported into secretory vesicles or degraded by monoamine oxidase (MAO)

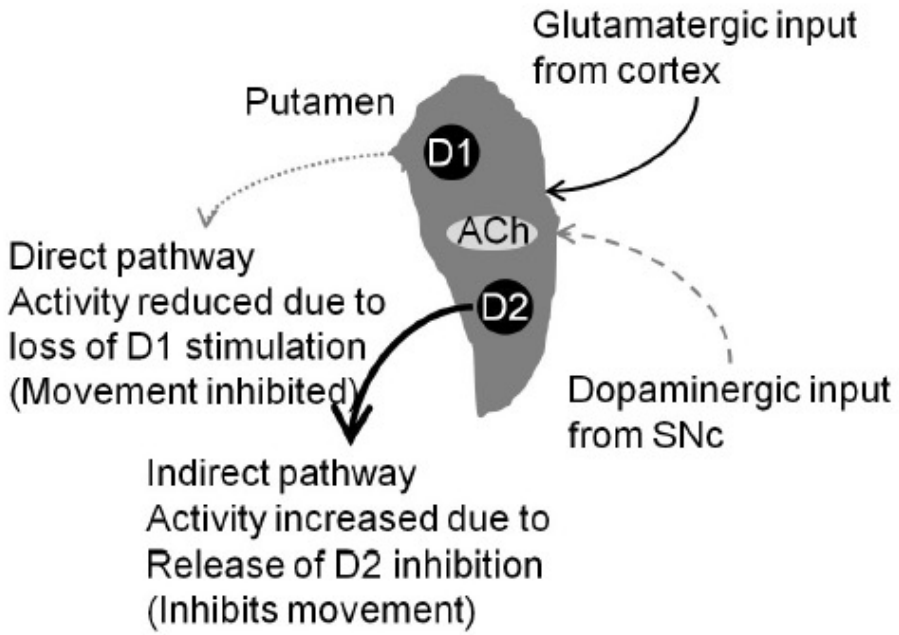


NEURAL MECHANISMS OF PARKINSONISM

Normal

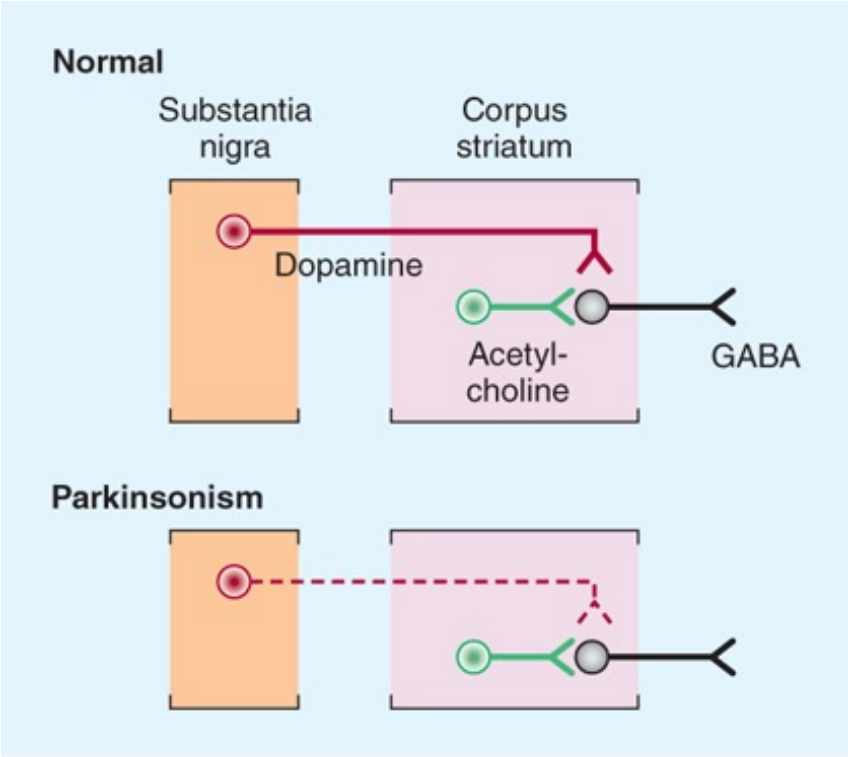


Parkinson's



SNc = nigrostriatal dopaminergic system

SIMPLIFIED CIRCUITRY IN PARKINSONISM



Source: Bertram G. Katzung, Todd W. Vanderah:
Basic & Clinical Pharmacology, Fifteenth Edition

Normal

Dopaminergic neurons (red) originating in the substantia nigra normally inhibit the GABAergic output from the striatum, whereas cholinergic neurons (green) exert an excitatory effect

Parkinsonism

In parkinsonism, there is selective loss of dopaminergic neurons (dashed, red) → ↓ dopaminergic transmission in striatum → loss of control of voluntary movements

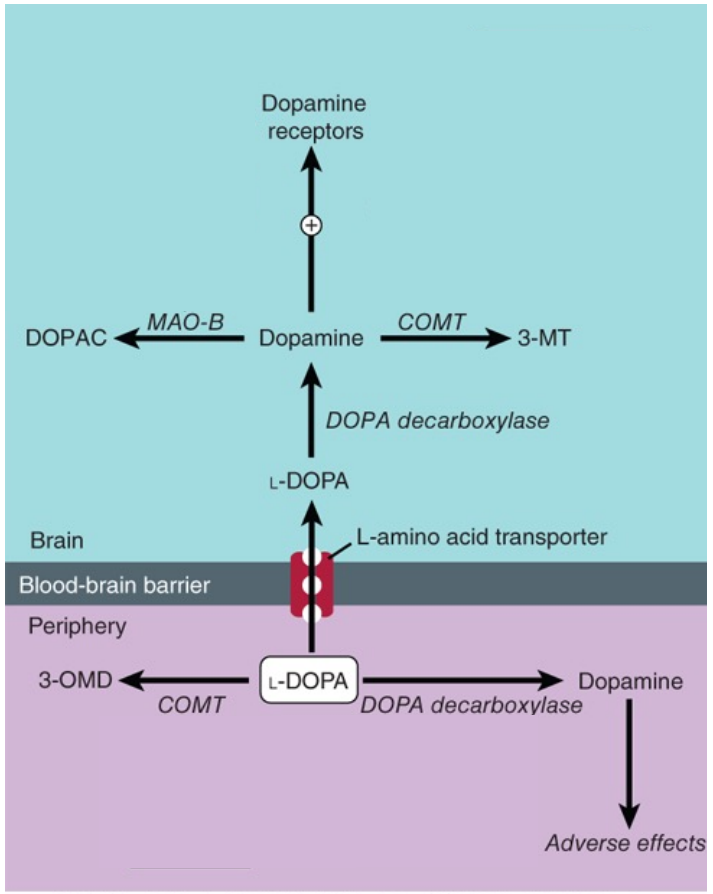
ACTIVE LEARNING

What is the most important neurotransmitter in Parkinson's Disease?

With this is mind, how might you modulate this neurotransmitter in the treatment of Parkinson's Disease?

ACTIVE LEARNING

Identify pharmacologic targets that may enhance the amount of dopamine receptors activated. Circle your identified targets on the diagram.



DRUG THERAPY FOR PARKINSON'S DISEASE

Salient pathophysiologic feature of Parkinson's Disease is the progressive loss of DA from the nigrostriatal tracts in the brain

Drug therapy aimed at REPLENISHING supply of DA

Exogenous DA

Inhibiting pathways that degrade levodopa and its metabolites

Stimulating DA receptors within the corpus striatum via DA agonists

Additional therapies

- Anticholinergics
- Amantadine

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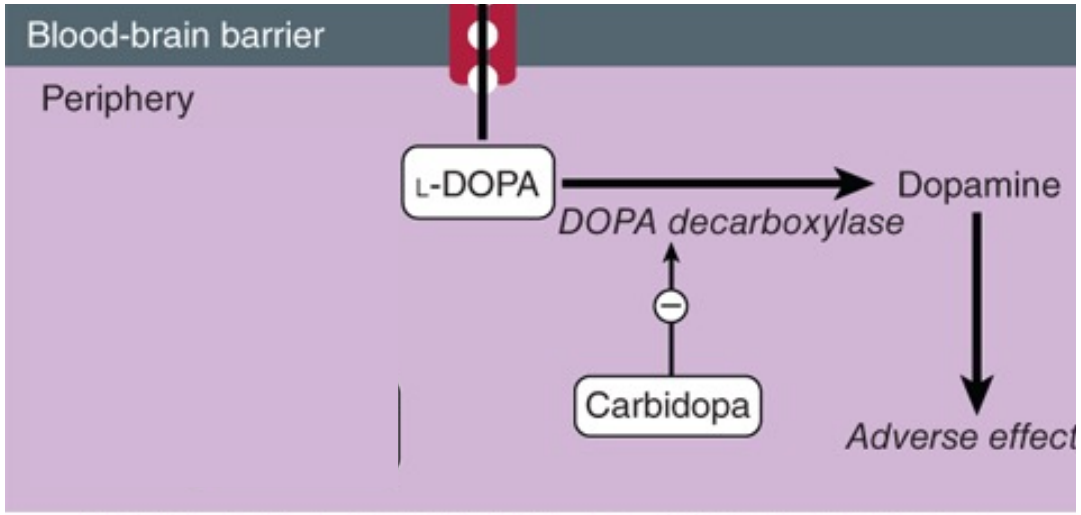
DOPAMINE PRECURSOR/DECARBOXYLASE INHIBITOR

Parkinson's Disease

CARBIDOPA-LEVODOPA MECHANISM OF ACTION

In periphery

- Levodopa (L-dopa) metabolized to DA by aromatic amino acid (dopa) decarboxylase
- Carbidopa is an inhibitor of dopa decarboxylase (does not cross the blood brain barrier)
- Combining levodopa with carbidopa enhances the amount of DA available to the brain and allows lower levodopa doses



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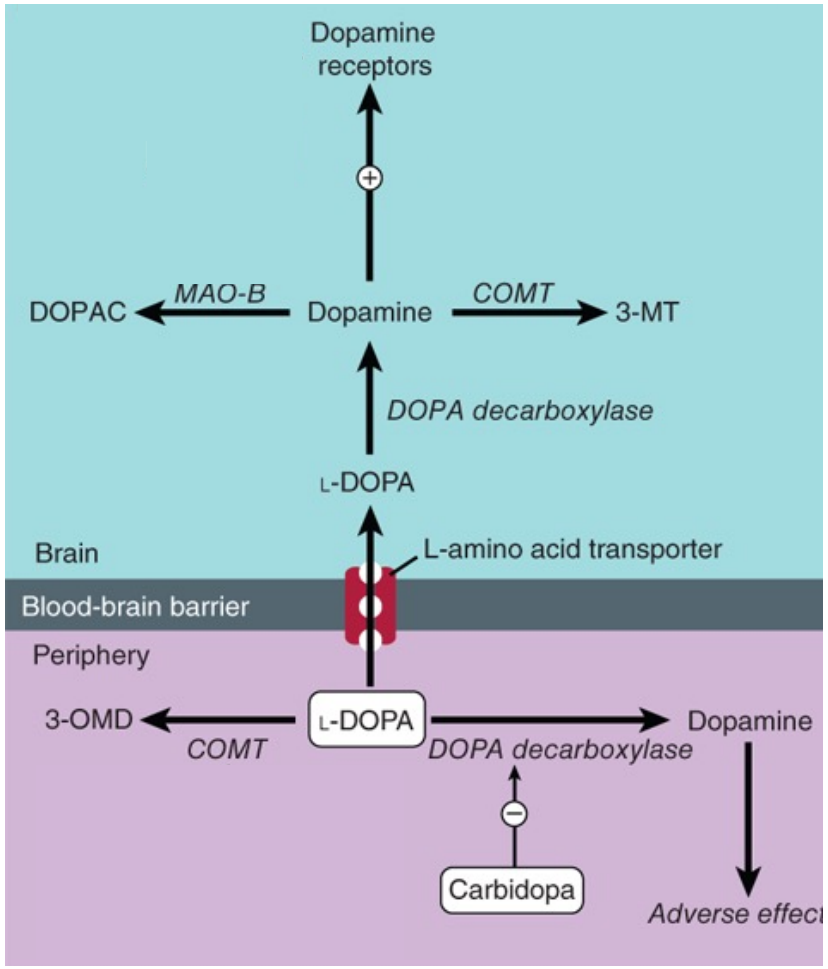
Katzung & Trevor's Pharmacology: Examination & Board Review, 13e

CARBIDOPA-LEVODOPA MECHANISM OF ACTION

Levodopa transported across blood-brain barrier by an amino acid transporter system

In the brain

- Levodopa converted to DA primarily in presynaptic terminals
- DA released from terminals to stimulate dopamine receptors
- D2 being the important receptor in treating Parkinson's disease



CARBIDOPA-LEVODOPA

Name	CIs & Cautions	Adverse Effects	Selected Interactions
Carbidopa-Levodopa (Sinemet)	**Concurrent use with MAOIs or use within last 14 days** **Glaucoma** Cautions: Somnolence, psychosis, melanoma	Discoloration urine/sweat Dizziness GI upset Impulse control disorders Motor fluctuations, dyskinesias Orthostatic hypotension Psychiatric effects Sleep attacks Mydriasis Impulse control disorders	Dietary amino acids can reduce levodopa absorption Nonspecific inhibitors of MAO (e.g., phenelzine) accentuate the actions of levodopa and may precipitate life-threatening hypertensive crisis ▪ Levodopa is converted to DA and subsequently norepinephrine ▪ MAOIs inhibit the degradation of DA

CARBIDOPA-LEVODOPA CLINICAL USE & ADME

Parkinson's disease

- First-line option

Multiple dosage forms (tablet, capsule, intestinal gel, oral inhalation)

Levodopa absorbed in proximal duodenum by an amino acid transporter system

When peripheral conversion to DA is blocked by carbidopa, the main route of metabolism is by COMT

All patients will require levodopa treatment at some point

LEVODOPA-INDUCED MOTOR COMPLICATIONS

Complications

1. Wearing off: shortened duration of beneficial effect from levodopa
2. Random off: lack of predictability of beneficial effect from levodopa
3. Freezing: loss of beneficial effect from levodopa for a period of time
4. Dyskinesias (e.g., chorea, dystonia): involuntary movements caused by levodopa use that happen more frequently during on-time than off-time

Strategies

Adjust levodopa dosing to address the specific motor complication (e.g., give longer-acting formulation in patients with wearing off)

Use a different formulation of levodopa (e.g., intestinal gel)

Add a COMT inhibitor, MAO-B inhibitor, or dopamine agonist to reduce off-time

Add amantadine for management of dyskinesias

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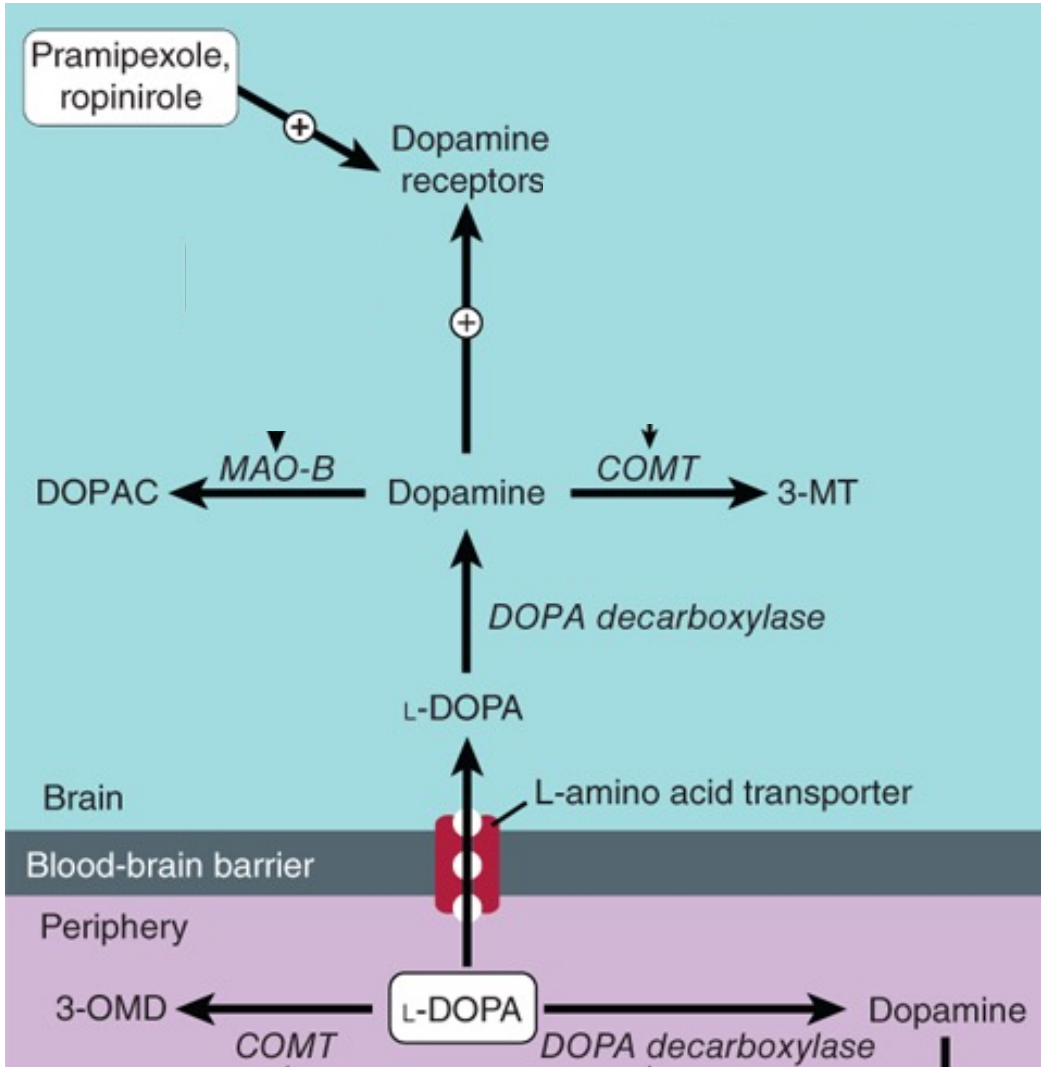
DOPAMINE AGONISTS

DOPAMINE AGONIST MECHANISM OF ACTION

Directly stimulate postsynaptic DA receptors within the corpus striatum

- Varying impact on specific receptors

Stimulation of D2 receptors largely responsible for reducing rigidity and bradykinesia



DOPAMINE AGONISTS

Name	CIs & Cautions	Adverse Effects	Selected Interactions
Pramipexole (Mirapex) **D3/D2 receptor affinity**	Psychotic illness Myocardial infarction Cautions: Renal dysfunction	CNS: Somnolence, hallucinations GI: Anorexia, **nausea**, vomiting CV: Postural hypotension Other: Motor complications, **impulse control disorders**	May enhance hypotensive effect of other medications
Ropinirole (Requip) **D2 receptor affinity**			Metabolized by CYP1A2, and other drugs metabolized by this isoform (eg, caffeine, warfarin) may reduce its clearance
Rotigotine **D2/D1**			May enhance hypotensive effect of other medications

OTHER DOPAMINE AGONISTS

Apomorphine

- Affinity High D4; moderate D2, D3, D5; low D1

Bromocriptine may be used, but typically not recommended due to adverse effects

DOPAMINE AGONIST CLINICAL USE & ADME

May be used as initial therapy

May delay introduction of levodopa

May be used with levodopa/carbidopa

Longer half-lives than levodopa/carbidopa

Rotigotine available as a patch

Apomorphine available as a subcutaneous injection (requires an antiemetic) and a sublingual film and requires a lower dose in renal impairment

Pramipexole requires dosage reduction in renal impairment

Withdrawal symptoms seen with discontinuation in 15-20% of patients (DAWS)

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CATECHOL-O-METHYLTRANSFERASE (COMT) INHIBITORS

CATECHOL-O-METHYLTRANSFERASE (COMT)

Enzyme within dopaminergic neurons

Degrades

- DA → 3-methoxytyramine (3-MT)
- Levodopa → 3-0-methyldopa

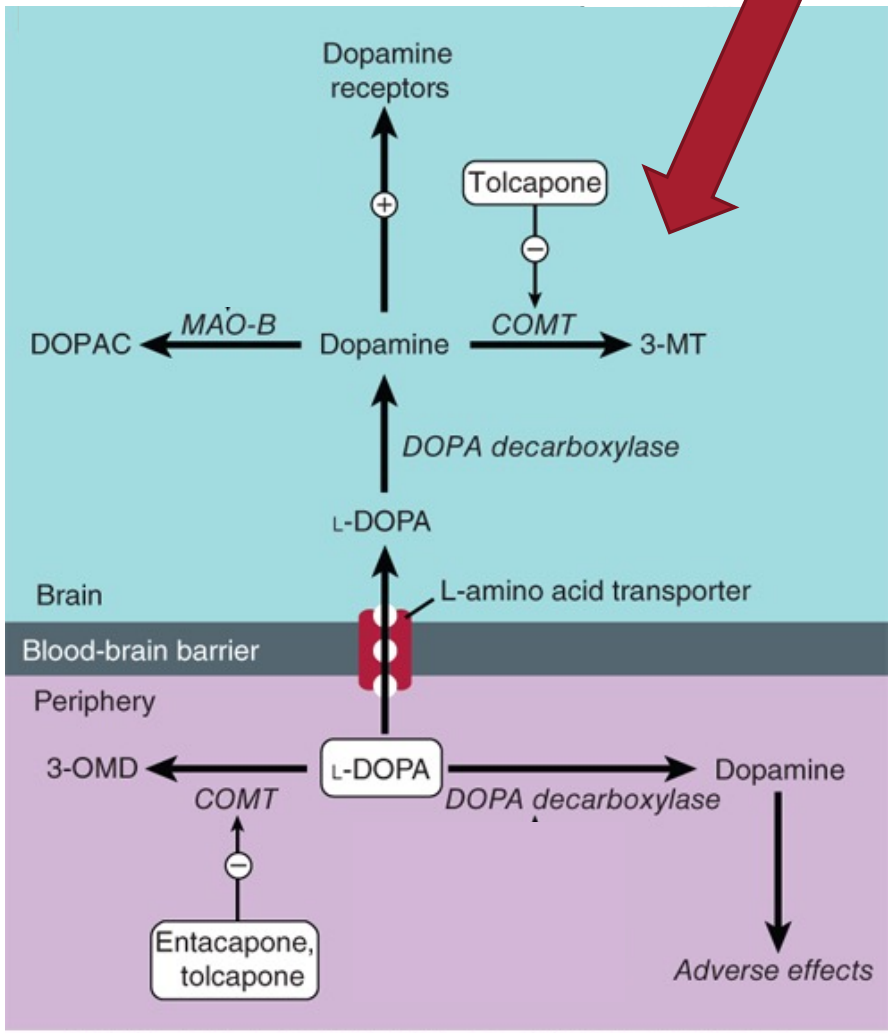
COMT INHIBITOR MECHANISM OF ACTION

Selective and reversible COMT inhibitors (inhibits conversion of DA to 3-MT)

Increase the amount of levodopa available for transport across the blood–brain barrier

- Tolcapone inhibits COMT in the periphery and in the CNS (also prevents dopamine degradation in the brain)
- Entacapone inhibits COMT in the periphery

Increases amount of "on" time and decreases levodopa dose needs



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COMT INHIBITORS

Name	CIs & Cautions	Adverse Effects	Selected Interactions
Entacapone (Comtan) *Periphery*	Cautions: CNS depressant use, alcohol use, hepatic impairment, psychosis history	CNS: Somnolence GI: Anorexia, nausea, vomiting CV: Postural hypotension Other: Motor complications **Urine discoloration (orange)**	May enhance CNS depression
Tolcapone (Tasmar) *Periphery and CNS*	Liver enzyme elevation Caution: Hepatic dysfunction, avoid while breastfeeding	**Same as entacapone PLUS** **May cause acute hepatic failure**	
Boxed warning: Tolcapone may cause hepatoxicity, including liver failure resulting in death			

ACTIVE LEARNING

Compare and contrast dopamine agonists and COMT inhibitors.

Now consider the COMT inhibitors entacapone and tolcapone. How are they similar? How are they different?

MONOAMINE OXIDASE (MAO)

MAO-A

MAO-A oxidatively deaminates catecholamines (serotonin, norepinephrine, tyramine)

MAO-B

MAO-B responsible for metabolism of DA

Can think "B" for "brain"

ACTIVE LEARNING

Consider monoamine oxidase (MAO) as a drug target for Parkinson's Disease. Would inhibiting or inducing MAO be useful in treating patients with Parkinson's Disease?

Do you think a nonselective, MAO-A selective, or MAO-B selective medication would be best for treating Parkinson's Disease? Defend your answer.

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MAO-B INHIBITORS

MAO-B INHIBITOR MECHANISM OF ACTION

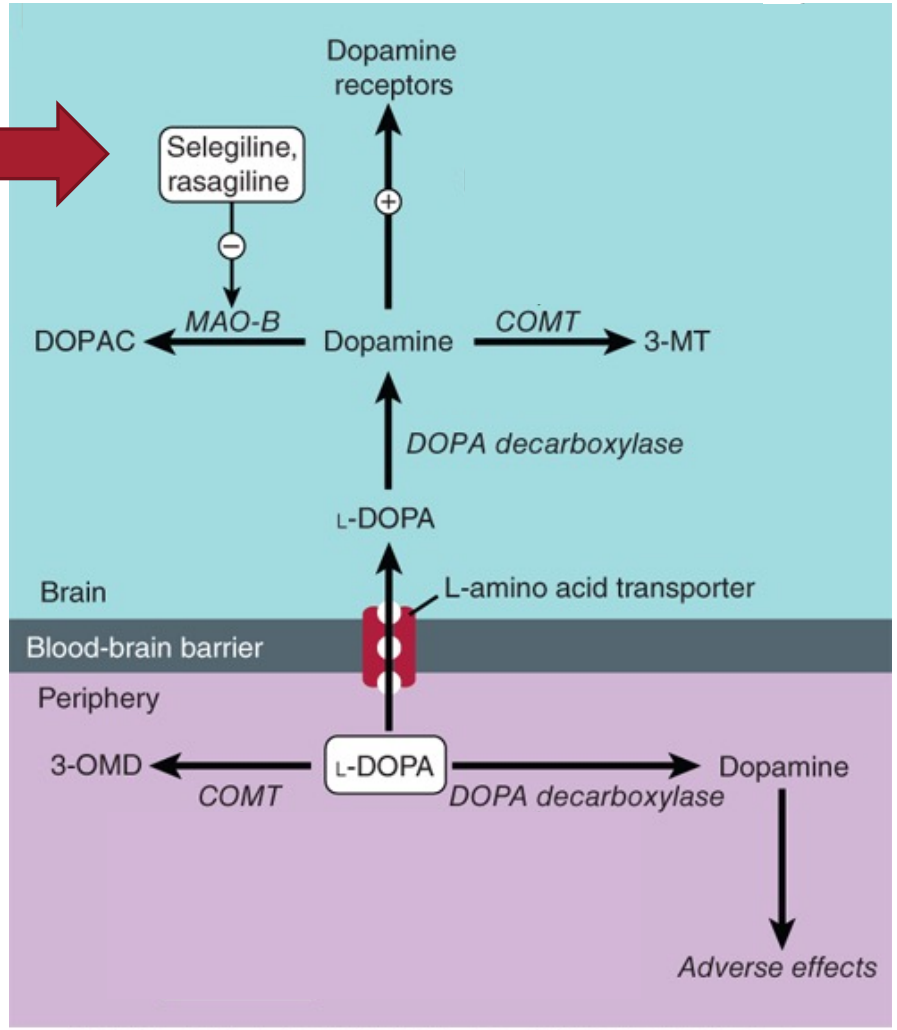
Inhibitors of MAO-B in the brain

- Selegiline, rasagiline are irreversible
- Safinamide is reversible

Prevents destruction of **endogenous and exogenous** DA

- Block conversion of DA to DOPAC

May be used as monotherapy or with levodopa



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MAO-B INHIBITORS

Name	CIs & Cautions	Adverse Effects	Selected Interactions
Rasagiline	Concurrent use or use within 14 days of MAOIs, meperidine, methadone, propoxyphene, or tramadol Concurrent use of cyclobenzaprine, dextromethorphan, or St John's wort Serotonin syndrome **Drug interactions**	CNS: Somnolence, hallucinations GI: Anorexia, nausea, vomiting CV: Postural hypotension Other: Motor complications	**Use with meperidine leads to agitation, delirium, and mortality** MAOIs may increase hypertensive effects of other drugs May enhance serotonergic effects of other drugs
Selegiline			
Safinamide			

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ADJUNCT THERAPIES

Parkinson's Disease

ACETYLCHOLINE

~5% brain neurons have receptors for acetylcholine (ACh)

Receptor Type	Receptor Mechanisms	Relevant Drugs
M1	Excitatory; ↓ K+ conductance; ↑ IP3 and DAG	Blocked by pirenzepine and atropine Muscarinic blocking inhibitors used in parkinsonism (benztropine)
M2	Inhibitory; ↑ K+ conductance; cAMP	Blocked by atropine
Nicotinic	Excitatory; ↑ cation conductance	Nicotine

ANTICHOLINERGIC MECHANISM OF ACTION

At homeostasis, there is balance between acetylcholine (ACh)- and DA-mediated neurotransmission

Loss of DA-producing neurons in Parkinson's Disease

- Results in loss of balance between ACh and DA

Anticholinergics block ACh (excitatory neurotransmitter) in the striatum

- Block muscarinic receptors
- Minimize effect of the relative increase in cholinergic sensitivity

May improve tremor and rigidity of parkinsonism but have little effect on bradykinesia. Anticholinergics are used adjunctively in parkinsonism and also alleviate the reversible extrapyramidal symptoms caused by antipsychotic drugs.

ANTICHOLINERGICS

Name	CIs & Cautions	Adverse Effects	Selected Interactions
Benztropine	Cautions: May cause anhidrosis and hyperthermia	Peripheral: dry mouth, blurred vision, constipation, urinary retention, increased intraocular pressure CNS: confusion, impairment of recent memory, hallucinations, delusions	May enhance anticholinergic effects of other drugs

AMANTADINE MECHANISM OF ACTION

An antiviral agent that has antiparkinsonian activity

Mechanism is not fully elucidated

- Augments DA release from presynaptic nerve terminals
- Possibly inhibits DA reuptake into storage granules
- Anticholinergic effects
- Antagonist at N-methyl-D-aspartate (NMDA) receptors

Add-on therapy for treating levodopa-induced dyskinesias

AMANTADINE

Name	CIs & Cautions	Adverse Effects	Selected Interactions
Amantadine	Cautions: End-stage renal disease, patients with melanoma	Neuropsychiatric complaints, which include dizziness, confusion, disorientation, depression, nervousness, irritability, insomnia, nightmares, and hallucinations **Livedo reticularis** Peripheral edema	May enhance CNS depressants effects of other CNS depressants

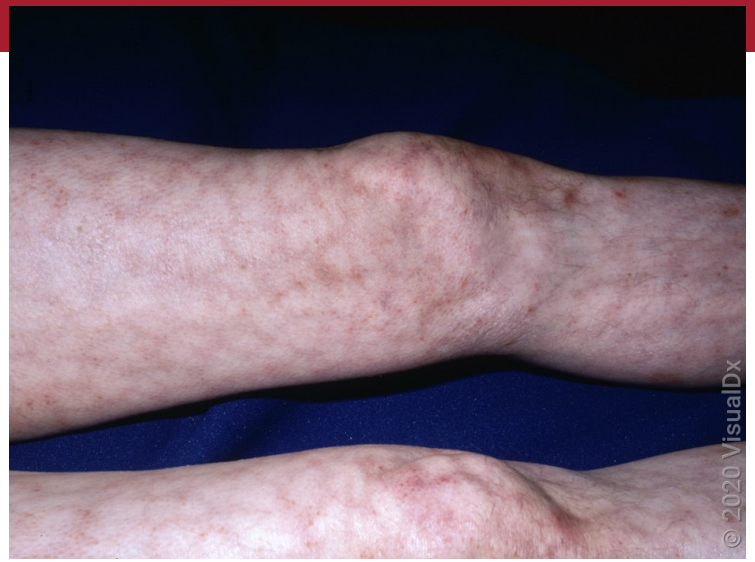
LIVEDO RETICULARIS

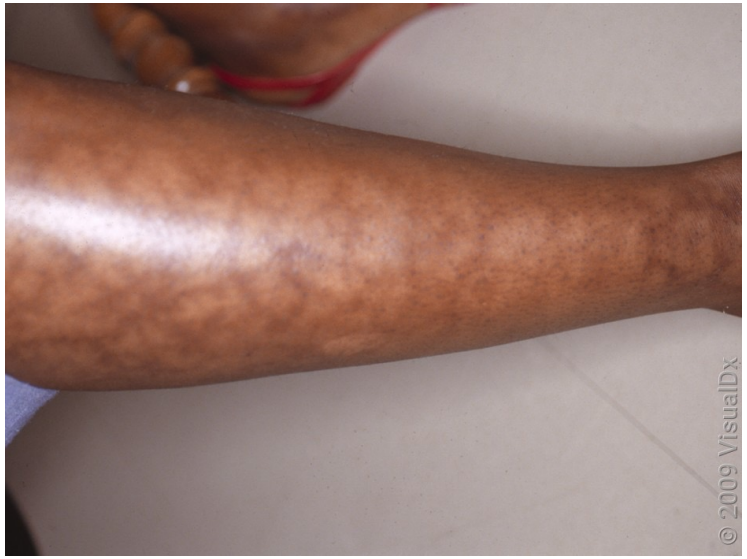
Rose-colored mottling of the skin

Usually involving lower extremities

Persists until therapy is discontinued

Caused by local release of catecholamines, which cause vasoconstriction and alter the permeability of cutaneous blood vessels





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DRUG-INDUCED PARKINSONISM

Drugs may cause parkinsonian symptoms (usually reversible)

Precipitating drugs

- Butyrophenone and phenothiazine antipsychotic drugs
  - Block brain dopamine receptors
- Reserpine
  - Depletes brain dopamine
- MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine), a byproduct of the attempted synthesis of an illicit meperidine analog, causes **irreversible** parkinsonism through destruction of dopaminergic neurons in the nigrostriatal tract

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ANY QUESTIONS?