Drugs Used in Parkinsonism

Pharmacology II

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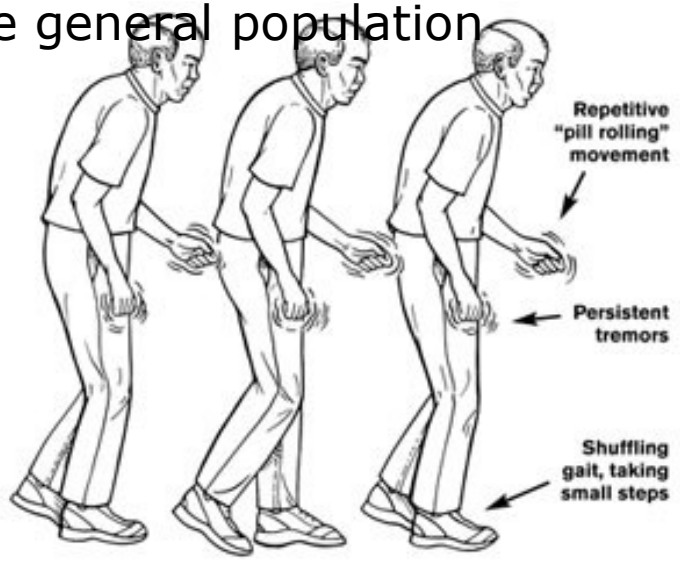
Parkinsonism

- Parkinsonism (Parkinson's disease): A progressive neurological disease characterized by tremor, rigidity, bradykinesis (sluggish neuromuscular responsiveness) and postural instability.

- It is first described by Dr. James Parkinson in 1817 as "shaking palsey".

- It has a prevalence of 1-2 per 1000 of the general population and 2 per 100 among people > 65 years.

- Generally occurs between age 50 and 65.



PARKINSON'S DISEASE

- Onset usually gradual, after age 50. (Slowly progressive)
- Mask-Like, Blank Expression
- Stooped Posture
- Pill Rolling Tremors

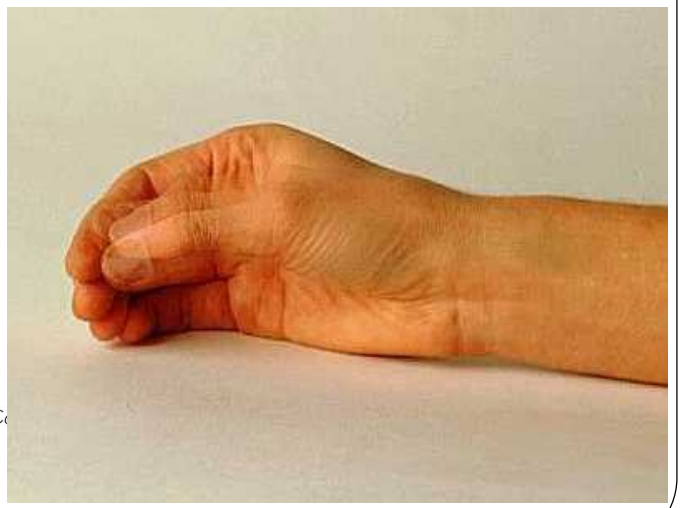
Bradykinesia
- Loss of normal arm swing while walking
- ↓ Blinking of the eyelids
- Loss of ability to swallow
- Blank expression
- Difficulty initiating movement

- Possible Mental Deterioration
- Depression

Tremor
- Commonly in hands and arm
- Pill rolling motion with the fingers
- Occurs most often at rest
- May involve diaphragm, tongue, lips and jaw
- Increases with stress

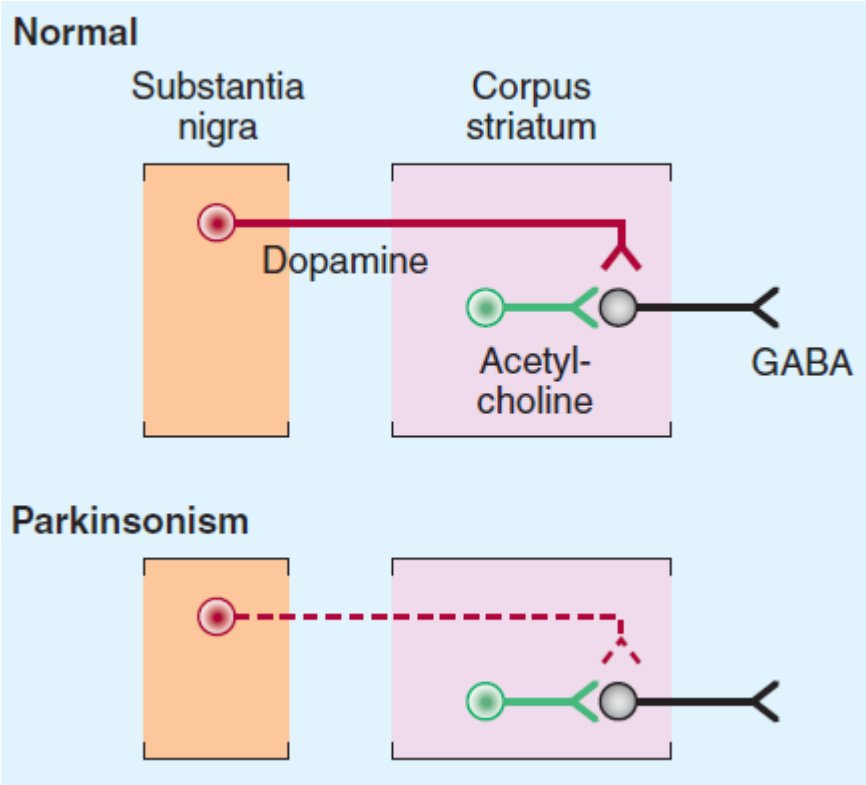
Muscle Rigidity
- ↑ Resistance to passive movement
- Cog wheel, jerky slow movement

- Rarely Occurs In Black Population
- Shuffling, Propulsive Gait



- Many of the symptoms of parkinsonism reflect an imbalance between the excitatory cholinergic neurons and the greatly diminished number of inhibitory dopaminergic neurons.

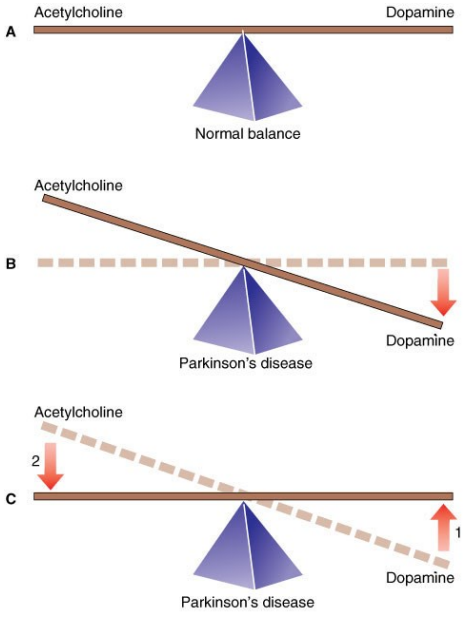
- Therapy is aimed at restoring dopamine in the basal ganglia and antagonizing the excitatory effect of cholinergic neurons, thus reestablishing the correct dopamine/acetylcholine balance.



Drug Therapy of Parkinsonism

- Strategies of drug treatment of parkinsonism involve increasing dopamine activity in the brain, decreasing muscarinic cholinergic activity in the brain, or both.

1. Levodopa/Carbidopa
2. Dopamine receptor agonists
3. Monoamine oxidase (MAO) inhibitors
4. Catechol-O-methyltransferase (COMT) inhibitors
5. Amantadine
6. Antimuscarinic drugs



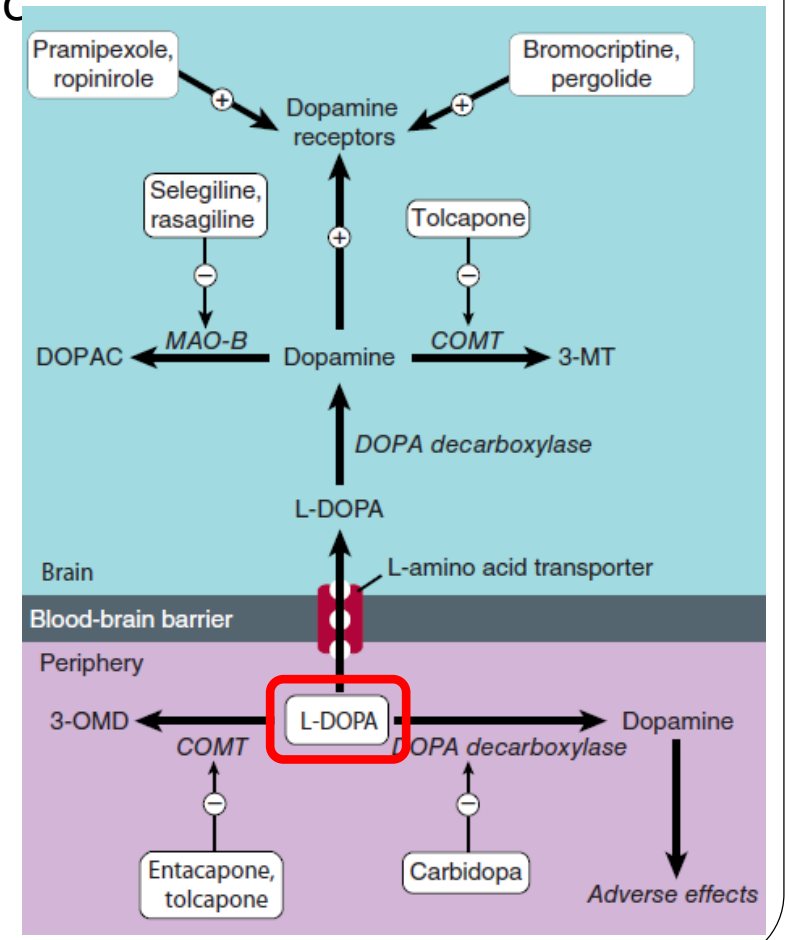
A, Normal balance of acetylcholine and dopamine in the CNS.
B, In Parkinson's disease, a decrease in dopamine results in an imbalance.
C, Drug therapy in Parkinson's disease is aimed at correcting the imbalance between acetylcholine and dopamine. This can be accomplished by either
1. increasing the supply of dopamine or
2. blocking or lowering acetylcholine levels.

Fig. 14-1. The neurotransmitter abnormality of Parkinson's disease.

1. Levodopa

- Dopamine does not cross the blood-brain barrier and if given into the peripheral circulation has no therapeutic effect in parkinsonism.

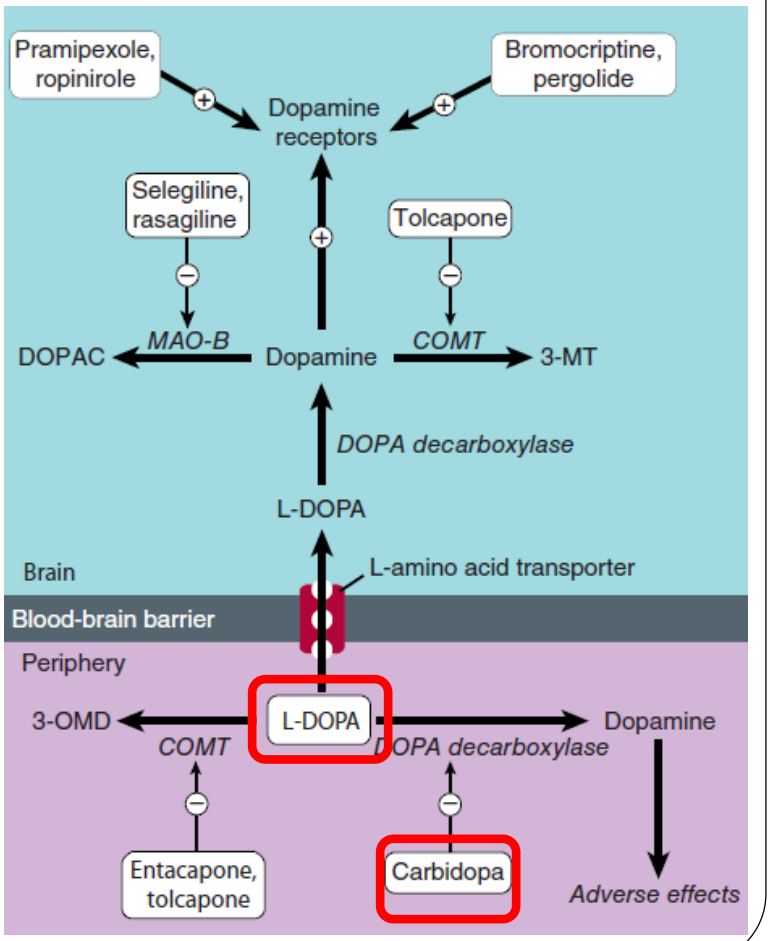
- However, **levodopa,** the immediate metabolic precursor of dopamine, does enter the brain (via an L -amino acid transporter, LAT), where it is decarboxylated to dopamine by the enzyme aromatic L-amino acid decarboxylase (dopa decarboxylase), which is present in many body tissues, including the brain.



1. Levodopa

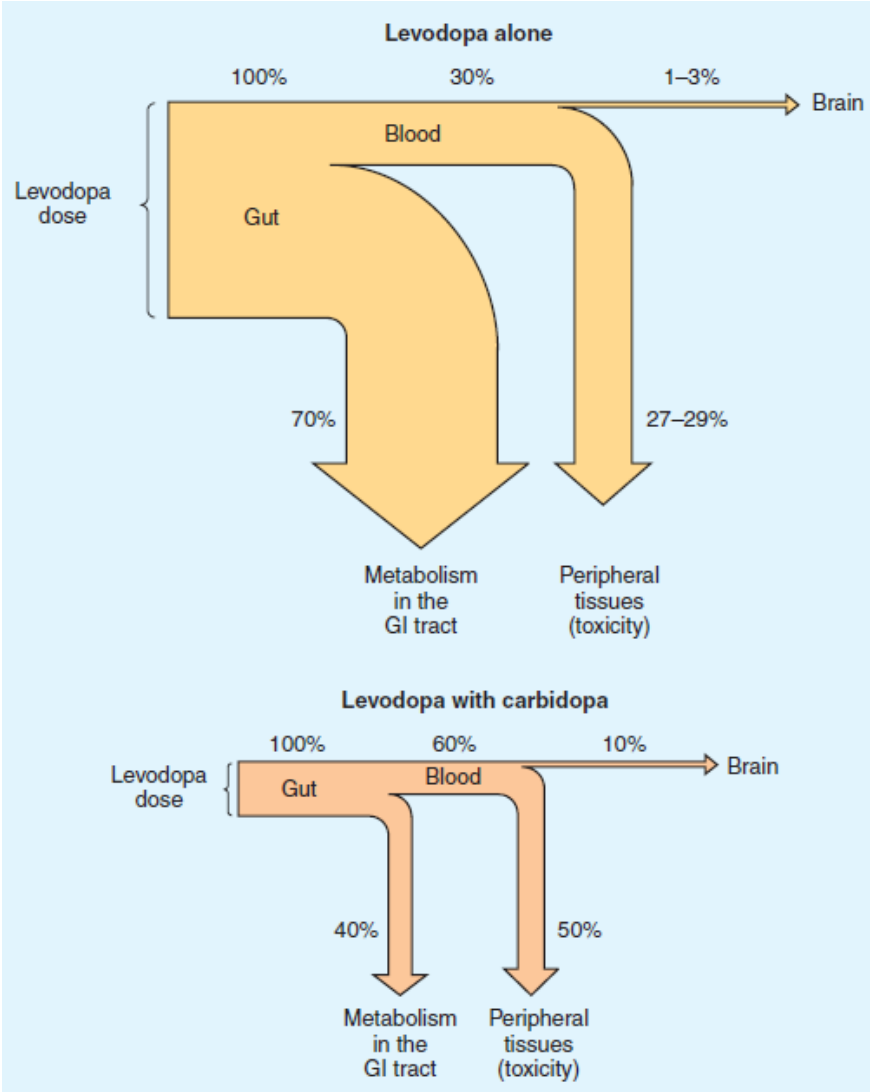
- Levodopa is usually given with **carbidopa** (a peripheral dopa decarboxylase inhibitor that does not cross the blood brain barrier), which diminishes the metabolism of levodopa in the gastrointestinal tract and peripheral tissues but not in the CNS, thereby increasing the availability of levodopa to the CNS.

- With this combination:
  - the plasma half-life is prolonged
  - lower doses of levodopa are effective
  - and there are fewer peripheral side effects.



1. Levodopa

- When levodopa is given alone, only about 1–3% of administered dose actually enters the brain unaltered.
- Concomitant administration of a peripheral dopa decarboxylase inhibitor such as carbidopa may reduce the daily requirements of levodopa by approximately 75%.



1. Levodopa

Absorption and metabolism:

- The drug is absorbed rapidly from the small intestine (when empty of food).
- Ingestion of food delays the appearance of levodopa in the plasma.
- Moreover, certain amino acids from ingested food can compete with the drug for absorption from the gut and for transport from the blood to the brain.
- Thus, levodopa should be taken on an empty stomach, typically 30-60 minutes before a meal.

1. Levodopa

- **Clinical Use**
- The best results of levodopa treatment are obtained in the first few years of treatment. The benefits of levodopa treatment often begin to diminish after about 3 or 4 years of therapy:

1. This is sometimes because the daily dose of levodopa must be reduced over time to avoid adverse effects at doses that were well tolerated initially.
2. In other cases, some patients become less responsive to levodopa, perhaps because of loss of dopaminergic nigrostriatal nerve terminals.

1. Levodopa

Pharmacologic effects:

- Effective in eliminating most of the symptoms of parkinson disease
  - Bradykinesia and rigidity respond quickly
  - Reduction in tremor effect with continued therapy
  - Handwritting , speech, facial expression and interest in life improves gradually

1. Levodopa

Adverse effects:

1. **Peripheral effects**:
    1. Anorexia, nausea, and vomiting due to stimulation of the chemoreceptor trigger zone of the medulla.
    2. Tachycardia result from dopaminergic action on the heart.
    3. Hypotension may also develop.

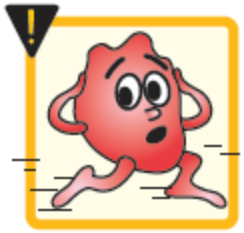
2. **CNS effects**: Visual and auditory hallucinations, mood changes, depression, and anxiety.

3. **Dyskinesia and response fluctuation:** "On-Off phenomenon" off-periods of marked akinesia (loss or impairment of voluntary movement) alternate over the course of a few hours with on-periods of improved mobility but often marked dyskinesia (abnormal involuntary movements).

Anorexia

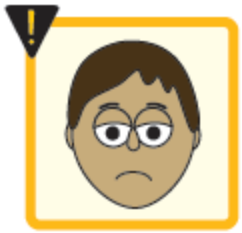
Nausea

Tachycardia



Hypotension

Psychiatric problems



1. Levodopa

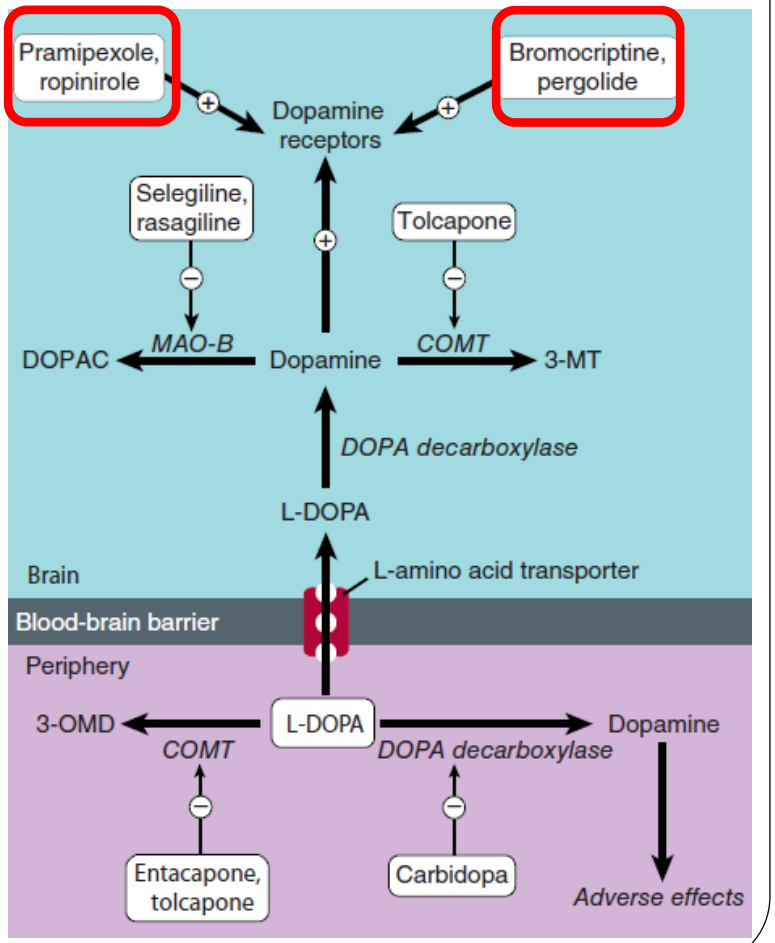
Drug interactions:

1. Pharmacologic doses of **pyridoxine (vitamin B6)** enhance the extracerebral metabolism of levodopa and may therefore prevent its therapeutic effect unless a peripheral decarboxylase inhibitor is also taken.

2. Levodopa should not be given to patients taking **monoamine oxidase A inhibitors**, such as phenelzine, or within 2 weeks of their discontinuance because such a combination can lead to hypertensive crises.

2. Dopamine Receptor agonists

- This group of anti-Parkinson compounds includes:
  - **Bromocriptine** and **pergolide**, are ergot derivative (rarely used).
  - **Ropinirole, pramipexole**, a newer, non-ergot drugs.
  - **Rotigotine** delivered daily through a skin patch, is approved for treatment of early Parkinson's disease.



2. Dopamine Receptor agonists

- These agents have durations of action longer than that of levodopa and, thus, have been effective in patients exhibiting fluctuations in their response to levodopa.

- However, these drugs are ineffective in patients who have shown no therapeutic response to levodopa.

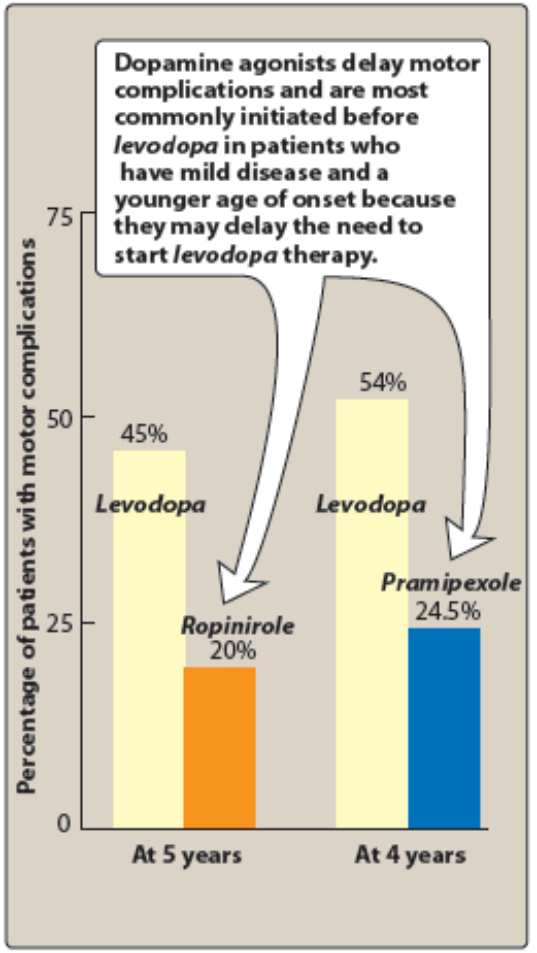
- **Apomorphine** is a potent dopamine receptor agonist, apomorphine injected **subcutaneously** may provide rapid (within 10 min) but temporary relief (1–2 h) of "off-periods" of akinesia in patients on optimized dopaminergic therapy.

2. Dopamine Receptor agonists

Pharmacologic Effects:

- Dopamine agonists may delay the need to use levodopa therapy in early Parkinson disease and may decrease the dose of levodopa in advanced Parkinson disease.

- Apomorphine is meant to be used for the acute management of the hypomobility "off" phenomenon.



2. Dopamine Receptor agonists

Adverse Effects:

- **Gastrointestinal Effects**
  - Anorexia and nausea and vomiting may occur when a dopamine agonist is introduced and can be minimized by taking the medication with meals.
- **Cardiovascular Effects**
  - Postural hypotension may occur, particularly at the initiation of therapy.
- **Dyskinesias**
  - Abnormal movements similar to those introduced by levodopa may occur and are reversed by reducing the total dose of dopaminergic drugs being taken.
- **Mental Disturbances**
  - Confusion, hallucinations, delusions, and other psychiatric reactions are potential complications of dopaminergic treatment and are more common and severe with dopamine receptor agonists than with levodopa.
  - various impulse control disorders (such as gambling disorders or compulsive shopping)

Sedation


Hallucinations

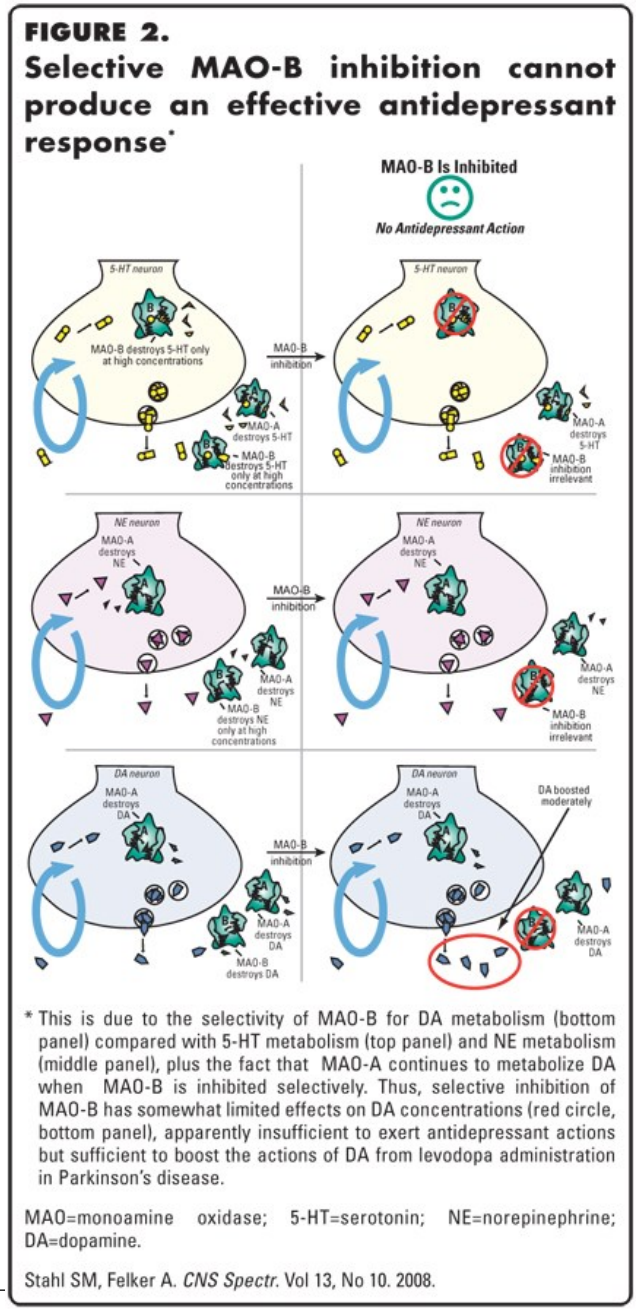
Confusion


Nausea

Hypotension

3. MAO-B Inhibitors

- Two types of monoamine oxidase have been distinguished in the nervous system:
  - **Monoamine oxidase A** metabolizes norepinephrine, serotonin, and dopamine.
  - **Monoamine oxidase B** metabolizes dopamine selectively.



3. MAO-B Inhibitors

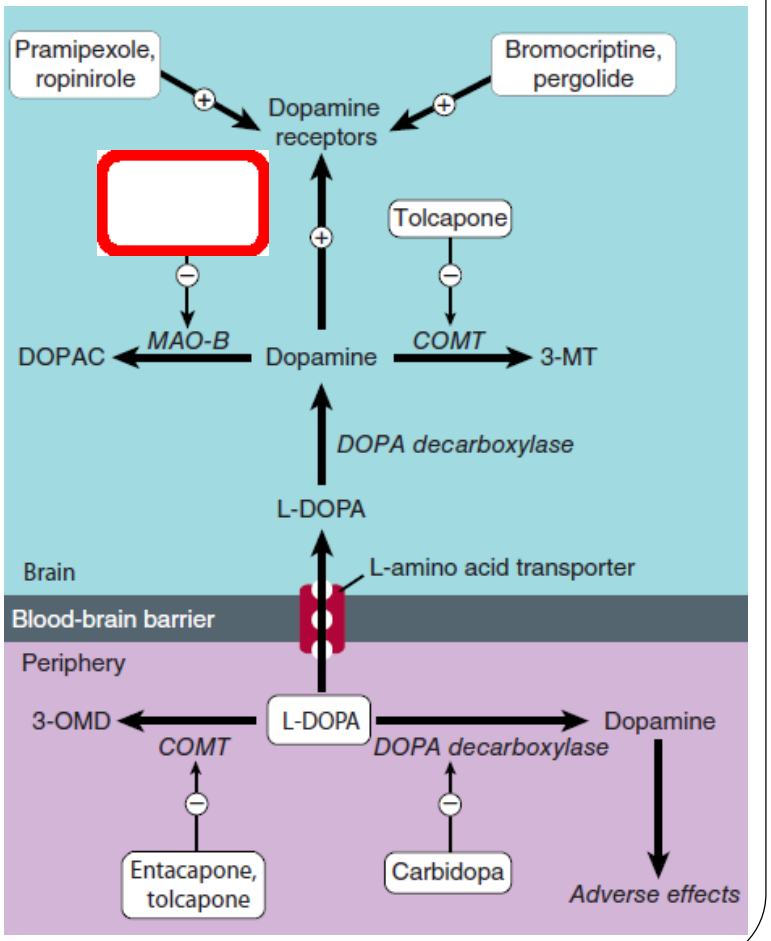
- **Selegiline** and **rasagiline** are selective inhibitors of monoamine oxidase type B, the form of the enzyme that metabolizes dopamine.

Clinical uses:

- Selegiline has minimal efficacy in parkinsonism if given alone but can be used adjunctively with levodopa.
- Rasagiline is more potent and has been used as monotherapy in early symptomatic parkinsonism as well as in combinations with levodopa.

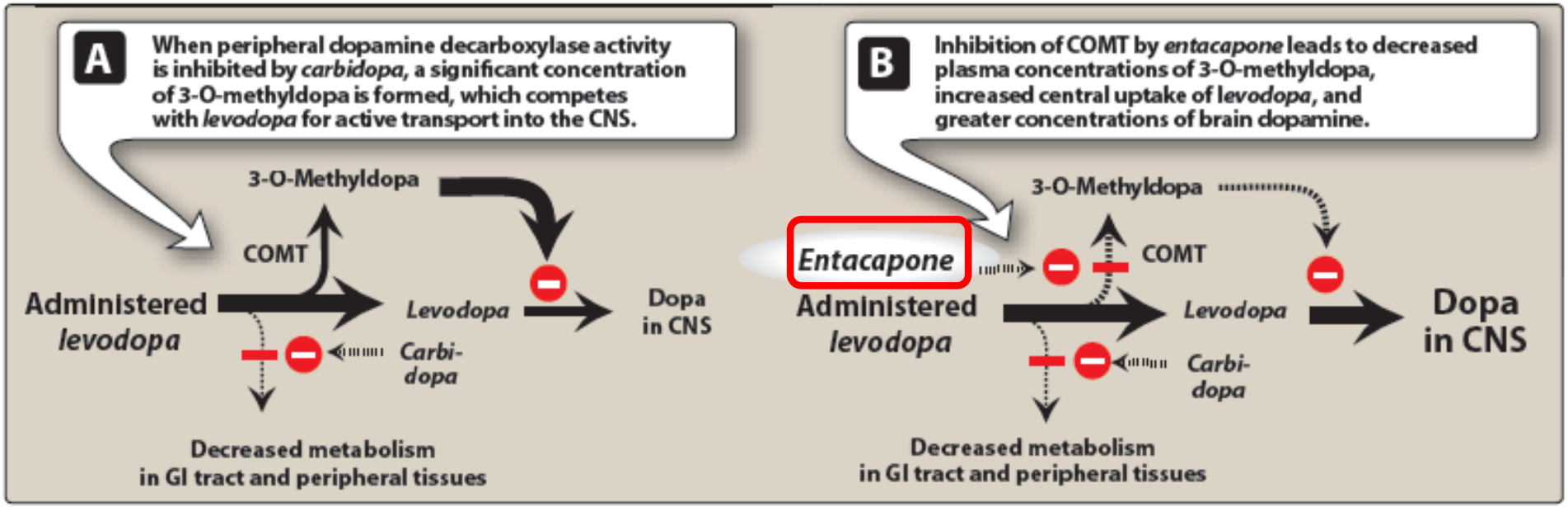
Adverse effects:

- Adverse effects of monoamine oxidase inhibitors include insomnia, mood changes, dyskinesias, gastrointestinal distress, and hypotension.



4. COMT 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.



4. COMT Inhibitors

- Inhibition of COMT by **entacapone** or **tolcapone** leads to decreased plasma concentrations of 3-O-methyldopa, increased central uptake of levodopa, and greater concentrations of brain dopamine. Both of these agents have been demonstrated to reduce the symptoms of "wearing-off " phenomena seen in patients on levodopa–carbidopa.

- Tolcapone has both central and peripheral effects, whereas the effect of entacapone is peripheral.

- Tolcapone is slightly more potent and has a longer duration of action.
  - Tolcapone is taken in a standard dosage of 100 mg three times daily; some patients require a daily dose of twice that amount. By contrast, entacapone (200 mg) needs to be taken with each dose of levodopa, up to five times daily.

4. COMT Inhibitors

Clinical uses:

- COMT inhibitors are used as adjuncts to levodopa-carbidopa, decreasing fluctuations and improving response.
- A formulation combining levodopa, carbidopa, and entacapone is available, simplifying the drug regimen.

Adverse effects:

- Adverse effects related partly to increased levels of levodopa include dyskinesias, gastrointestinal distress, and postural hypotension.
- Levodopa dose reductions may be needed for the first few days of COMT inhibitor use.
- Other side effects include sleep disturbances and orange discoloration of the urine.
- Tolcapone increases liver enzymes and has reports of fatal liver toxicity, necessitating routine monitoring of liver function tests.

5. Amantadine

- **Amantadine**, an antiviral agent, was by chance found to have antiparkinsonism properties.
- Its mode of action in parkinsonism is unclear, but it may potentiate dopaminergic function by influencing the synthesis, release, or reuptake of dopamine.
- The drug also has muscarinic blocking actions, requiring a decrease in the dosage of the anticholinergic drugs when amantadine is added.

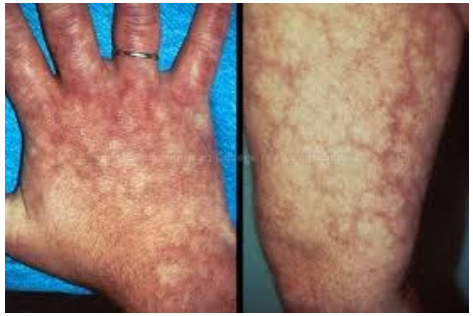
Pharmacologic effects:

- **Amantadine** may improve bradykinesia, rigidity, and tremor but is usually effective for only a few weeks.
- The standard dosage is 100 mg orally two or three times daily.

5. Amantadine

Adverse effects:

- Amantadine has a number of undesirable central nervous system effects, all of which can be reversed by stopping the drug. These include restlessness, agitation, insomnia, confusion, hallucinations. With doses several times higher than recommended, convulsions have occurred.
- **Dermatologic reactions** include livedo reticularis, a diffuse rose-color mottling of the skin, and usually clears within 1 month after the drug is withdrawn.
- **Miscellaneous effects** may include gastrointestinal disturbances, urinary retention, and postural hypotension.
- Amantadine also causes peripheral edema, which responds to diuretics.
- Amantadine should be used with caution in patients with a history of seizures or heart failure.



6. Anti-muscarinic Drugs

- A number of centrally-acting antimuscarinics (eg, benztropine, biperiden, orphenadrine) decrease the excitatory actions of cholinergic neurons on cells in the striatum by blocking muscarinic receptors.
- **Pharmacologic effects:**
- These drugs are more effective for tremor and rigidity of parkinsonism but have little effect on bradykinesia. They are used adjunctively in parkinsonism.
- Treatment is started with a low dose of one of the drugs in this category, the dosage gradually being increased until benefit occurs or until adverse effects limit further increments.
- If patients do not respond to one drug, a trial with another member of the drug class is warranted and may be successful.

TABLE 28–1 Some drugs with antimuscarinic properties used in parkinsonism.

Drug	Usual Daily Dose (mg)
Benztropine mesylate	1–6
Biperiden	2–12
Orphenadrine	150–400
Procyclidine	7.5–30
Trihexyphenidyl	6–20

6. Anti-muscarinic Drugs

Adverse effects:

- CNS toxicity includes drowsiness, inattention, confusion, delusions, and hallucinations.
- Peripheral adverse effects are typical of atropine-like drugs which include dry mouth (hard candies may be helpful); decreased sweating, resulting in decreased tolerance to heat; urinary retention; constipation and increased intraocular pressure.
- If medication is to be withdrawn, this should be accomplished gradually rather than abruptly to prevent acute exacerbation of parkinsonism.

General Comments on drug management of patient with parkinsonism

- When symptomatic treatment becomes necessary, a trial of rasagiline, amantadine, or an antimuscarinic drug (in young patients) may be worthwhile.
- With disease progression, dopaminergic therapy becomes necessary. This can conveniently be initiated with a dopamine agonist, either alone or in combination with low-dose carbidopa-levodopa therapy (25/100 three times daily).
- Alternatively, especially in older patients, a dopamine agonist can be omitted and the patient started immediately on carbidopa-levodopa.
- Most patients ultimately require carbidopa 25 mg, levodopa 250 mg three or four times daily.

CASE STUDY

A 64-year-old architect complains of left-hand tremor at rest, which interferes with his writing and drawing. He also notes a stooped posture, a tendency to drag his left leg when walking, and slight unsteadiness on turning. He remains independent in all activities of daily living. Examination reveals hypomimia (flat facies), hypophonia, a rest tremor of the left arm and leg, mild rigidity in all limbs, and impaired rapid alternating movements in the left limbs. Neurologic and general examinations are otherwise normal. What is the likely diagnosis and prognosis? He is started on a dopamine agonist, which he seems to tolerate well, and the dose is gradually built up to the therapeutic range. About a year later, he and his wife return for follow-up. It now becomes apparent that he is spending large sums of money, which he cannot afford, on gambling and refuses to stop, despite his wife's entreaties. To what is his condition due and how should it be managed?

CASE STUDY ANSWER

The relation of the tremor to activity (rest tremor) in this case is characteristic of parkinsonism. Examination reveals the classic findings of Parkinson's disease—rest tremor, rigidity, bradykinesia, and a gait disturbance; an asymmetry of the abnormalities is common in Parkinson's disease. The prognosis is that symptoms will become more generalized with time. Pharmacologic treatment would involve a dopamine agonist (pramipexole or ropinirole) but may not need to be started now unless the patient is disturbed by his symptoms. The patient developed an impulse control disorder (gambling) after starting on an agonist, and this may require dose reduction or discontinuation of the agonist.

Questions??