Drugs for Neurodegenerative Disorders

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Neurodegenerative Disorders

- **Parkinson's disease.**
- **Huntington's disease**, excessive and abnormal movements resulting from the loss of a specific subset of striatal neurons.
- **Alzheimer's disease**, an injury in the hippocampus and cortex.
- **Amyotrophic lateral sclerosis (ALS),** a progressive weakness and muscle atrophy due to degeneration of spinal, bulbar, and cortical neurons.

Parkinsonism

Paralysis Agitans , 1817

Gait.

Bradykinesia = Poor movements,

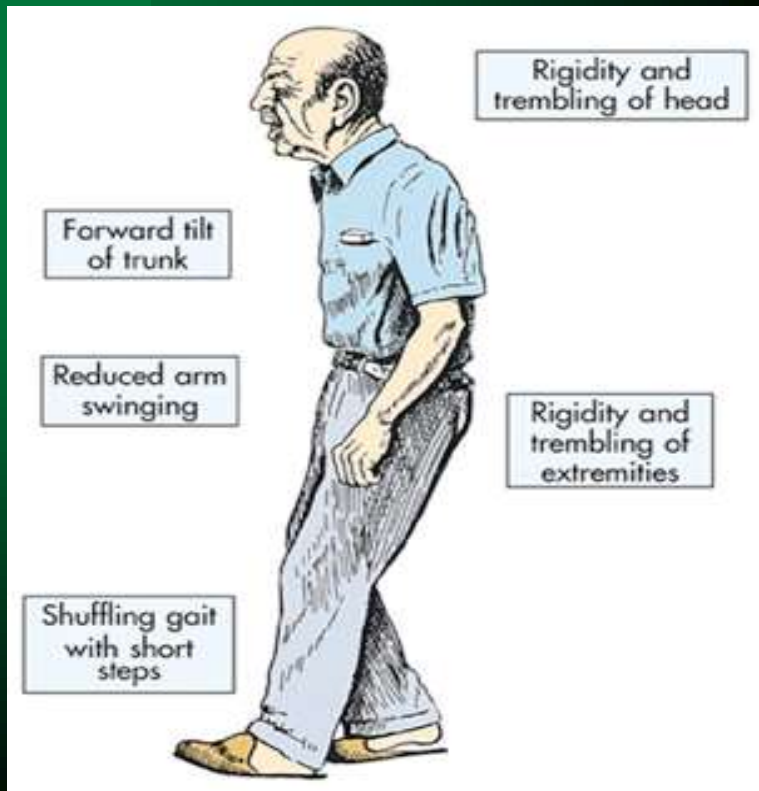
Mask- like Facies

Resting Tremor.

Rigidity: Cog-wheel type.

Cognitive decline,

depression, and dementia.



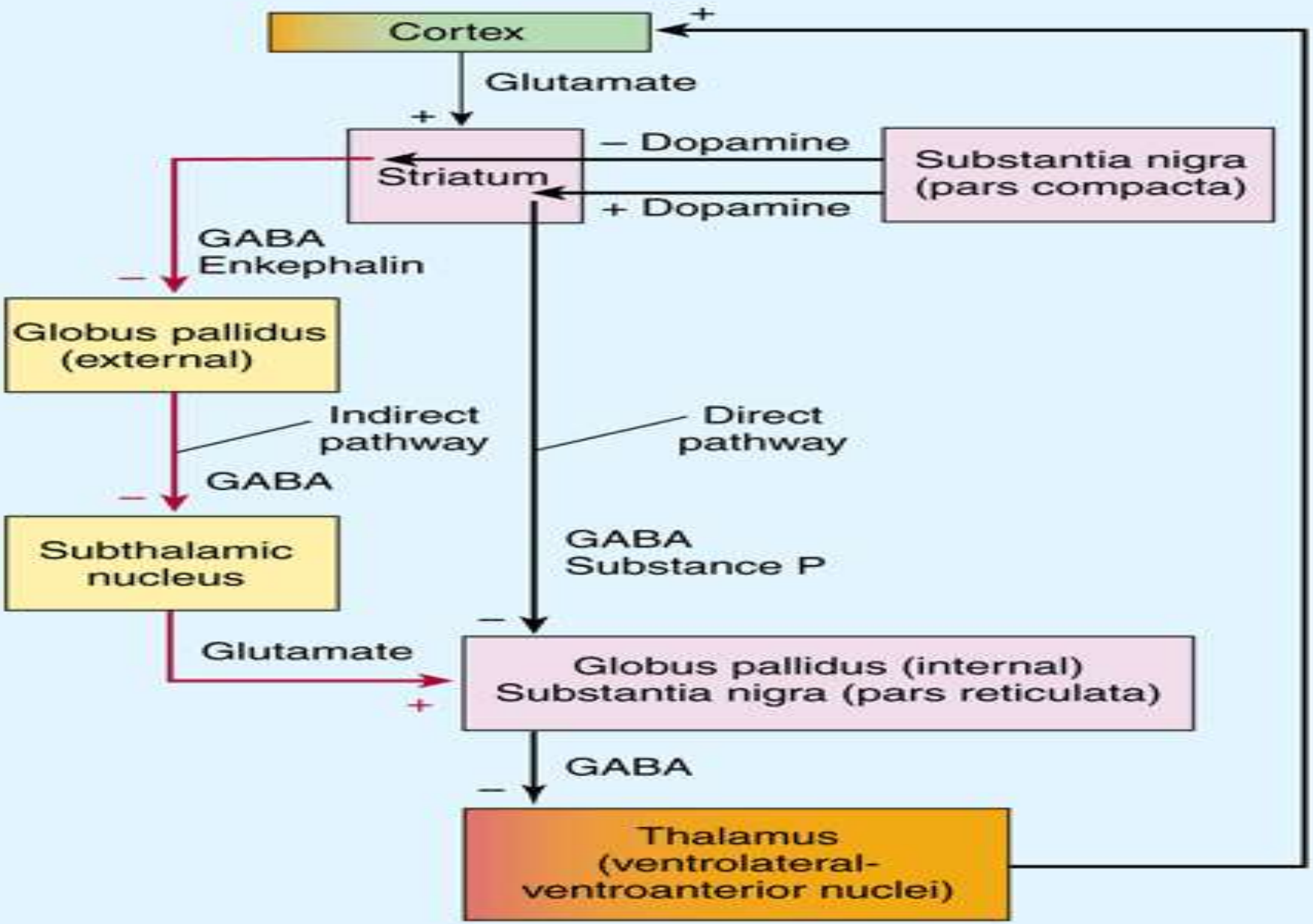
Etiology of Parkinsonism

- **Postencephalitic.**
- **Arterioselerotic.**
- **Autoimmune**
- **Poisoning:** **Free radicals, CO, Mn++, Wilson's Disease.**

  MPTP, a synthetic byproduct of a meperidine analog, is a protoxin converted into MPP+ which leads to cell death and premature parkinsonism.
- **Drugs:** **Antipsychotics.**

  Reserpine.

  α-Methyl Dopa
- **Idiopathic:? Multifactorial, genetic factors, Aging**



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Pathology of Parkinsonism

- Neuron destruction in Globus Pallidus
- Dark pigmentation of Substantia Nigra.
- Reduced basal ganglia levels of Dopamine and 5HT.
- The presence of inclusion bodies ”Lewy Bodies”.

Biochemistry and Pharmacology of Movement Disorders.

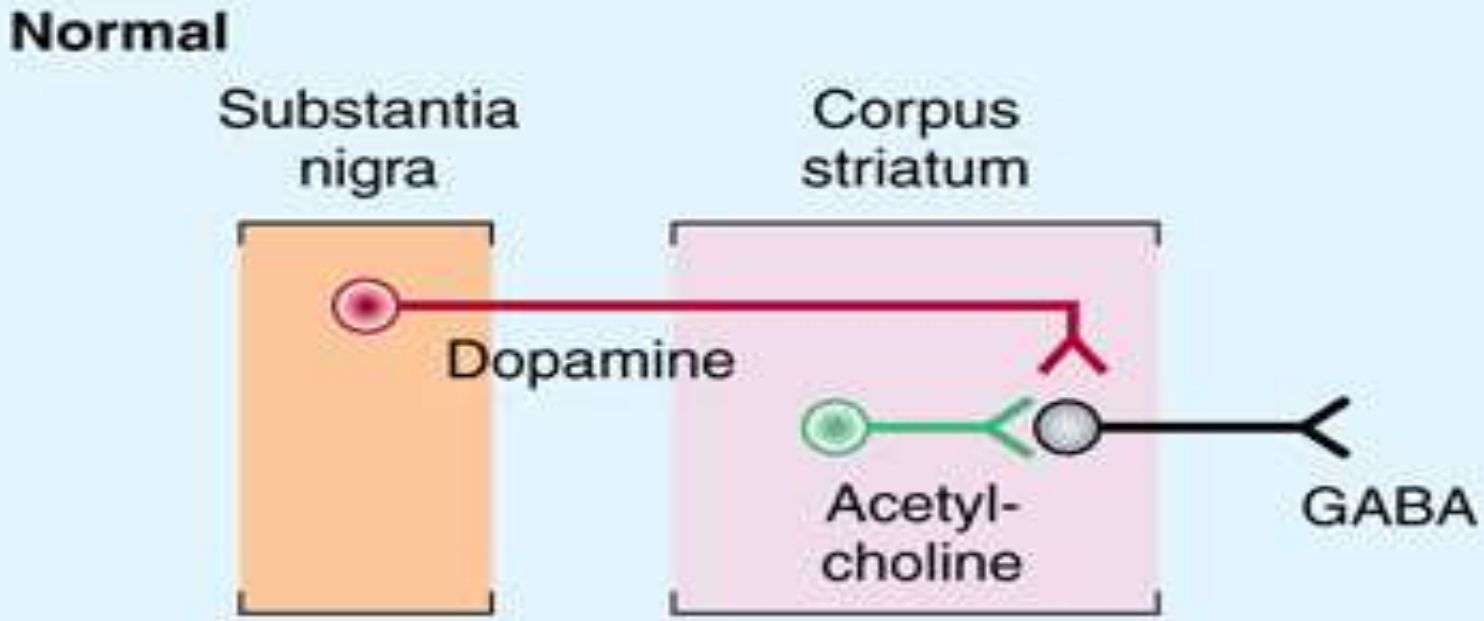
- Cholinergic ---------- Dopaminergic
  (Facilitatory) (Inhibitory)

Parkinsonism:

- Loss of dopaminergic neurons in S.N., which normally inhibit the output of GABAergic cells in the corpus striatum.

Huntington's Chorea:

Loss of cholinergic neurons and greater loss of GABAergic cells that exit the corpus striatum.



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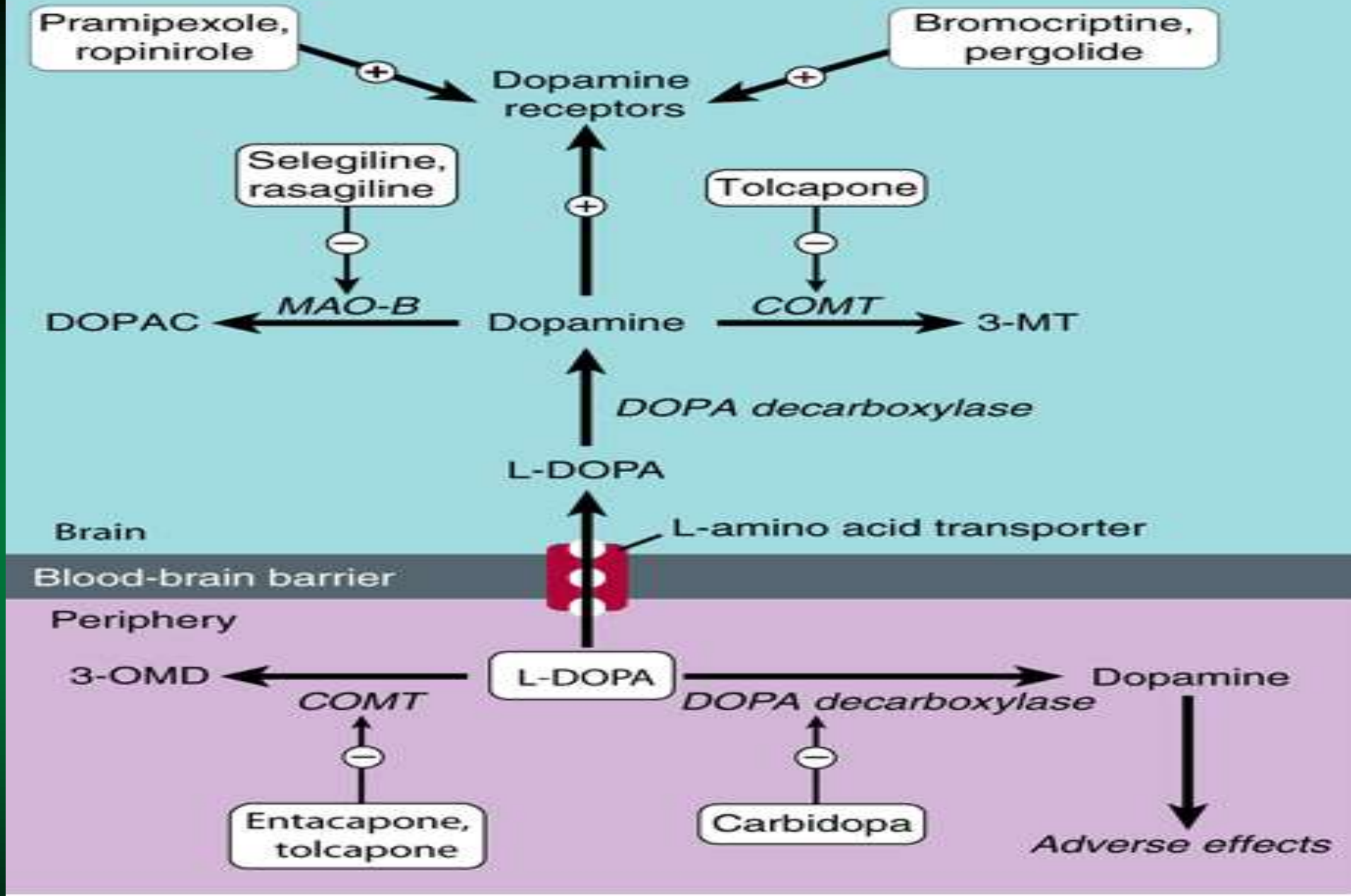

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L-Dopa or Levodopa

- The most reliable and effective drug used in the treatment of parkinsonism.
- Considered a form of replacement therapy.
- The precursor of dopamine.
- Used to elevate dopamine levels in the neostriatum of parkinsonian patients.
- Dopamine itself does not cross BBB.
- Levodopa, is transported into the brain where it is converted to dopamine.

L.Dopa or Levodopa

- Rapidly absorbed from g.i.t., delayed by food.
- Dietary amino acids can compete for absorption and for transport into the brain.
- Levodopa is rapidly metabolized in the brain to Dopamine by Decarboxylase.

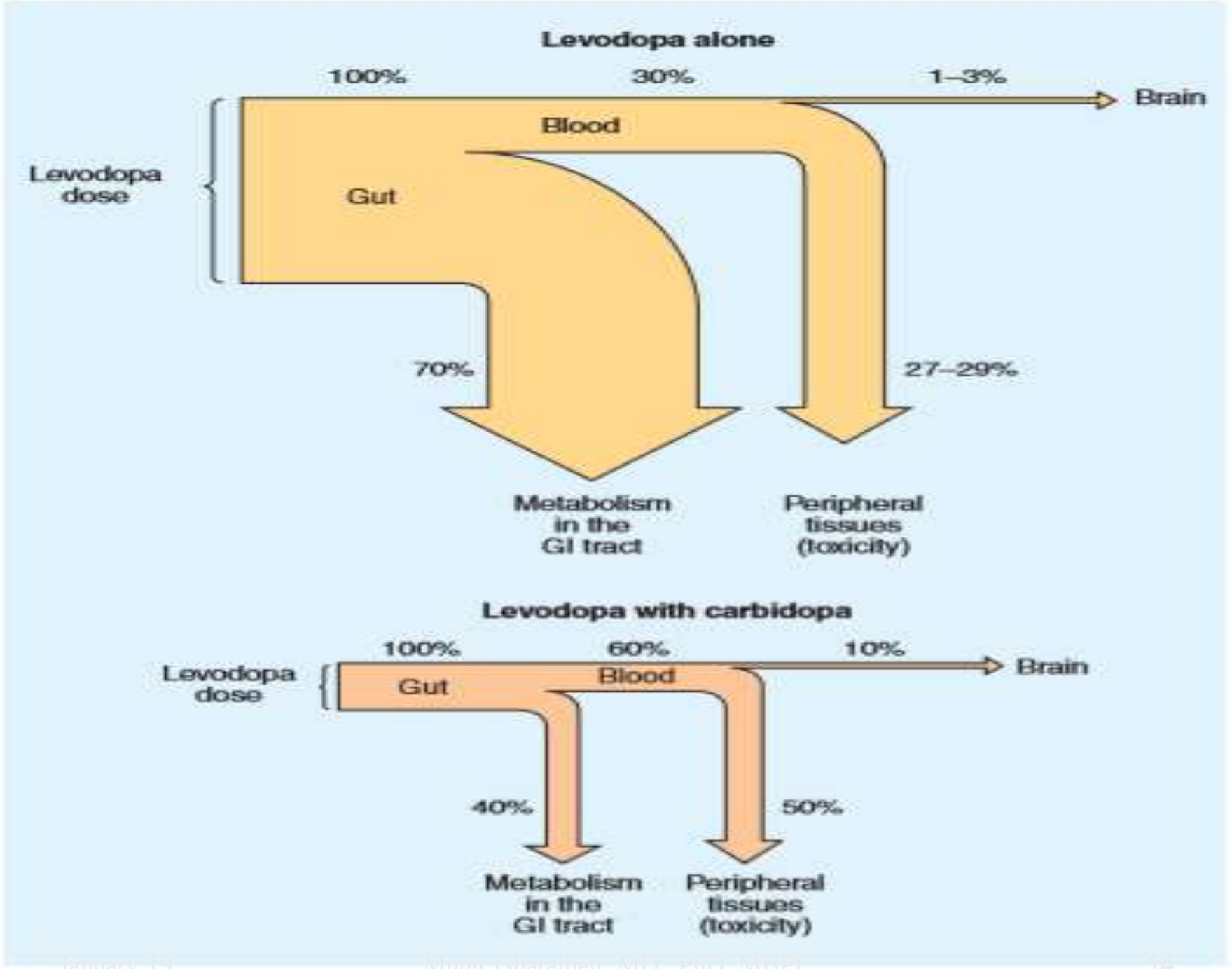
Levodopa

- Levodopa is also Alpha, Beta1 and Dopa receptor agonist.
- D2 presynaptic receptor stimulation inhibits NE release, so --------- Hypotension(Neurogenic Postural Hypotension).

Carbidopa and Benserazid

- Can not cross BBB.
- Inhibit (LAAD) Decarboxylase, peripherally.
- When combined with levodopa, the daily required dose of levodopa is reduced by 75% and its peripheral conversion to dopamine and toxicity is reduced.

- Levodopa + Carbidopa = "Sinemet"
- 10/100 , 25/100, 25/250


Levodopa alone
100%
30%
1–3%
Brain
Blood
Levodopa dose
Gut
70%
27–29%
Metabolism in the GI tract
Peripheral tissues (toxicity)
Levodopa with carbidopa
100%
60%
10%
Brain
Levodopa dose
Gut
Blood
40%
50%
Metabolism in the GI tract
Peripheral tissues (toxicity)

Clinical Use of Levodopa+Carbidopa

- Very useful for 3-4 years.
- Does not stop the progression of the disease, but lowers the mortality.
- One third of the patients respond very well and one third less well.
- Remainder either are unable to tolerate the drug or do not respond at all.
- Responsiveness may ultimately be lost completely, perhaps because of the disappearance of dopaminergic nigrostriatal nerve terminals, or some direct pathologic process of the receptors.

Side Effects of Levodopa

- **Gastrointestinal Effects:**

Anorexia, Nausea, Vomiting:

Due to stimulation of CTZ, but do not give phenothiazines.

Occur in 80%. So, give after meals or in divided doses or give antacids.

- **Cardiovascular Effects:**

Postural Hypotension, tachycardia, extrasystoles, atrial fibrillation, hypertension with high doses or with MAO inhibitors.

Side Effects of Levodopa

Dyskinesias: 80%

Choreoathetosis of the face and distal extremities is the most common. Variable among patients.

- **Behavioral Effects:**

Depression, anxiety, agitation, delusions, hallucinations, confusion, disorientation, insomnia, somnolence, nightmares, euphoria, and others.

May be precipitated by intercurrent illness or surgery.

Side Effects of Levodopa

- **Fluctuations in Response:**

Wearing –off Reactions or End-of-Dose Akinesia.

On-off Phenomenon:

Marked dykinesia alternating over the course of a few hours with on-periods of improved mobility.

Mechanism unknown.

Apomorphine injection might help.

Side Effects of Levodopa

- **Miscellaneous Effects:**

Mydriasis might lead to acute glaucoma.

Blood dyscrasias, hemolysis, +ve Coomb'sTest

Hot flushes, Gout, abnormalities of smell or taste, brownish discoloration, priapism, high urea, transaminases, AlkPhase and bilirubin.

Levodopa

- **Drug Holidays:**
- *No longer recommended.*

May temporarily improve responsiveness to levodopa and alleviate some of its adverse effects, but not the on-off phenomenon.

However, carries the risks of aspiration pneumonia, venous thrombosis, pulmonary embolism and depression.

Levodopa

- **Contraindications:**

  Psychotic patients.

  Angle-closure glaucoma.

  Active peptic ulcer disease.

  History of melanoma or undiagnosed skin lesion.

Dopamine Receptor Agonists

- Directly stimulate dopamine receptors and do not depend on the formation of dopamine from levodopa.
- None is superior to others.
- Variable response of patients.
- Lower incidence of fluctuations and dyskinesias.

Dopamine Receptor Agonists

- Considered as the **first approach** to therapy.
- Less effective than levodopa but are often used early in the disease to delay initiation of levodopa therapy.
- Have long duration of action.
- Less likely to cause dyskinesia than levodopa.
- Can be used as an adjunct to levodopa in advanced stages, to improve the condition and reduce dose of levodopa.

Dopamine Receptor Agonists

- **Bromocriptine:**
  - D2 agonist.
  - Ergot derivative.
  - Can cause pulmonary & retroperitoneal fibrosis.

- **Pergolide:**
  - D2 and D1 agonist.
  - Also ergot derivative.
  - Valvular heart disease.

Dopamine Receptor Agonists

- **Pramipexole:**

  D3>D2 agonist, non ergot.

- **Ropinirole:**

  D3>D2 agonist, non ergot .

  May ameliorate affective symptoms.

  Possible neuroprotective action: scavenge hydrogen peroxide.

Adverse Effects of Dopamine Receptor Agonists

Gastrointestinal Effects:

Anorexia, nausea, vomiting, constipation, dyspepsia, reflux esophagitis, bleeding ulcer.

Cardiovascular Effects:

Postural hypotension, digital vasospasm, arrhythmias, edema, valvopathy.

Dyskinesias.

Mental disturbances:

More than with levodopa.

Others:

Headache, nasal congestion, *erythromelalgia*, narcolepsy.

Apomorphine

- Potent dopamine agonist.
- Effective for temporary relief of off-on periods of akinesia of patients on dopaminergic therapy.
- Action starts within 10 minutes of injection and lasts for up to 2 hours.
- Causes nausea, vomiting, dyskinesia, drowsiness, sweating, hypotension and bruising at injection site.

MAO Inhibitors

Selegilline = Deprenyl:

- Irriversible inhibitor of MAO-B.
- For newly diagnosed cases who have some endogenous DA.
- Also combined with Levodopa --- to decrease the doses and fluctuations.
- May retard the progression of the disease by an antioxidant activity.

  ?Inhibits the f*ormation of a toxic product in DA metabolism.*
- Also, its metabolite has a neuroprotective effect by an antiapoptotic mechanism.

Rasagiline:

MAO-B inhibitor, more potent.

Neuroprotective.

COMT Inhibitors

- Inhibition of dopa decarboxylase is associated with compensatory activation of COMT leading to increased 3OMD, which competes with levodopa for its transport.
- So, COMT inhibitors can prolong the action of levodopa by diminishing its peripheral metabolism.
- Increase the “on-time” .
- Reduce the daily dose of levodopa.

COMT Inhibitors

- **Entacapone:**

  Has peripheral effects.

- **Tolcapone:**

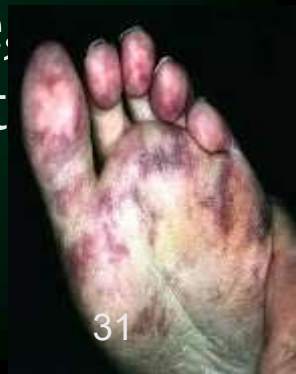
  Has central and peripheral effects.

  Can cause fulminant hepatic necrosis.

Amantadine

- Antiviral
- Enhances the synthesis, release or reuptake of DA.
- Also has antimuscarinic and NMDA receptor antagonistic activity.
- Effects are short –lived.
- Used occasionally, to help in reducing iatrogenic dyskinesias.

- Can cause excitement, hallucinations and confusion, edema, *livedo reticularis*, headache, heart failure, postural hypotension, urinary retention and g.i.t disturbances.



Anticholinergic Drugs

Belladona Alkaloids:

- **Atropine:** Less CNS depression , in high doses can cause stimulation
- **Scopolamine:** Drowsiness, euphoria.

Synthetic Alkaloids:

- **Trihexylphenidyl**
- **Benztropine**
- **Biperiden**
- **Orphenadrine**

Anticholinergic Drugs

- * Mild and early stages.
- *Block muscarinic receptors in the striatum.
- * For tremor and rigidity more than dyskinesia.
- * Good for drug induced parkinsonism.
- * Elevate the mood.
- * Block sialorrhea.
- * Tolerance, but no cross tolerance.
- * Minimal systemic effects: Cycloplegia, Dryness, suppurative parotitis, Retention, Constipation, Confusion, Delirium, Hallucinations.

Antihistamines

- Diphenhydramine
- Orphenadrine
- Chlorphenoxamine

- * Most effective against rigidity
- * Mood elevation _____ Euphoria
- * Sedation
- * Weak peripheral anticholinergic actions

Neuroprotective Therapy

- Antioxidants.
- Antiapoptotic Agents.
- Glutamate antagonists.
- Glial-derived neurotrophic factor.
- Coenzyme Q10
- Creatine.
- Antiinflammatory agents.

Gene Therapy

- Trials involved infusion into the striatum of adeno-associated virus type 2 as the vector for the gene.
- Genes were produced for glutamic acid decarboxylase (GAD), to facilitate synthesis of GABA, for aromatic acid decarboxylase (AADC), and for neurturin (a growth factor that may enhance the survival of dopaminergic neurons).

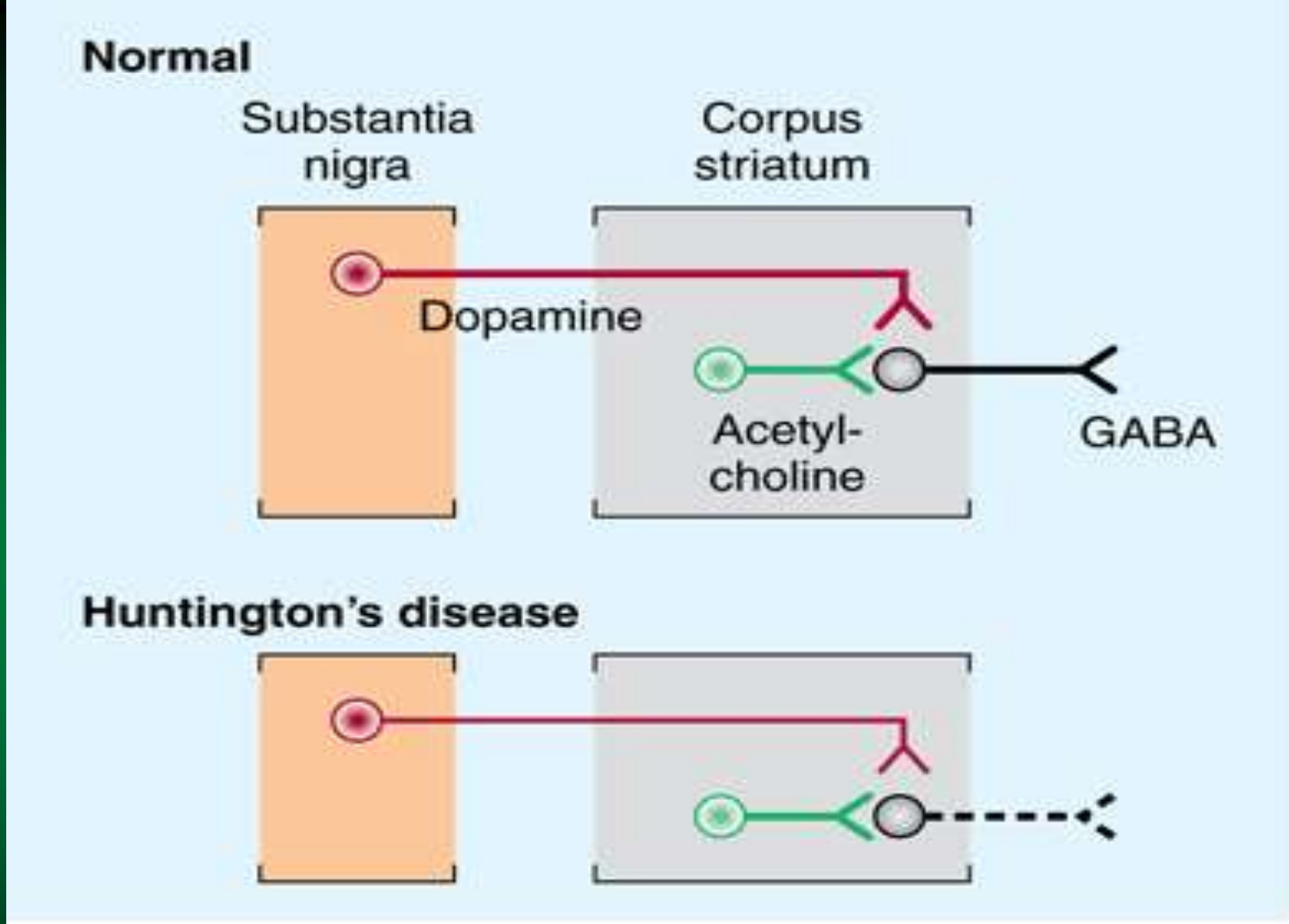
Surgery

- **Ablation of the ventral intermediate nucleus of the thalamus for tremor.**
- **Ablation of the posteroventral portion of globus pallidus for dyskinesia.**
- **Electrical stimulation of thalamus, subthalamic nucleus or globus pallidus.**
- **Fetal substantia nigra transplantation.**
- **Stem cell transplant.**

Can result in relative excess of dopamine from continued fiber growth from the transplant.

Huntington’s Disease(Chorea)

- An inherited disease causing progressive breakdown (degeneration) of nerve cells in the brain, with an impact on functional abilities resulting in movement, thinking (cognitive) and psychiatric disorders.
- Signs and symptoms appear in the 30s or 40s. But the disease may emerge earlier or later in life.
- Juvenile Huntington's disease develops before 20's.



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ALZHEIMER'S DISEASE

- Alzheimer's disease is the most prevalent form of dementia.
- Afflicts approximately 10% of the population over age 65.
- Loss of memory.
- Disordered cognitive function.
- Alterations in behavior and a decline in language function.
- In advanced stages, the individual may not recognize spouse or children, levels of arousal and alertness are severely impaired, with reduced verbal fluency.
- Ultimately, motor function is impaired and the patient may fall into a vegetative state.
- Death is usually associated with complications of immobility (e.g., pneumonia or pulmonary embolism).

Pathology of Alzheimer's Disease

- Loss of cholinergic neurons and acetylcholine in the brain.
- Affected brain regions include the entorhinal cortex(الناصية); hippocampus; amygdala; association cortices of the frontal, temporal and parietal lobes; and subcortical nuclei that project to these regions.
- Hallmarks are βamyloid and τ tangles (causal or byproducts).

Drugs for Alzheimer Disease

Acetylcholinesterase Inhibitors:

- Only palliative, do not cure or prevent the disease.
- **Tacrine:**
  - First useful drug.
  - Many other actions on release and receptors of MAO, GABA, NE, DA, 5HT.
  - Only delays further decline.
  - Hepatotoxic, NVD.
- **Donepezil**
- **Galantamine**
- **Rivastigmine**

Drugs for Alzheimer Disease

- **Memantine:**

  NMDA receptor antagonist.

  May slow progression of the disease.

  Less toxic.

- **Future Directions:**

  Molecules that prevent the proteolytic cleavage of amyloid precursor protein

  Antibodies to remove the A β peptides from the cells and brain.

  Antiinflammatory agents and antioxidants.