Landmarks in understanding Parkinson’s disease:

- **The 1st anti-hypertensive drug was reserpine** → which is depleting dopamine → leading to manifestations of extrapyramidal tract lesion.
- **Chlorpromazine is a drug used in treating patients with schizophrenia** → is a dopamine receptor blocker → also producing manifestations of extrapyramidal tract lesion.
- **A history of some patients in US who used heroin contaminated with MPTP** → which is destroying dopaminergic neurons → inducing Parkinson’s disease. Note: from these 3 conditions, you can notice that Parkinson’s disease is mainly related to deficiency of dopamine.

The deficiency in dopamine render cholinergic neurons unchecked → therefore, there will be increased release of Ach → leading to imbalance of circuits (formation of reverberating circuits) → extrapyramidal system problem (hypokinesia, lead-pipe rigidity and tremor at rest).

Therapeutic strategies in Parkinson’s disease:

- **Administering the precursor (L-DOPA) → levodopa is given orally to the patient.**
  - Levodopa is the cornerstone treatment for Parkinson’s disease.
  - Levodopa is given in combination with carbidopa in 2 forms:
    - *Either sinemet.*
    - *Or sinemet-CR:* in which there is sustained release of the drug.
    
    **Note:** levodopa is converted to dopamine outside the central nervous system → this dopamine will cause cardiac side effects and it cannot cross the blood-brain barrier and thus not reaching the brain → therefore a decarboxylase inhibitor which will inhibit peripheral decarboxylation but does not cross the blood-brain barrier (allowing decarboxylation in CNS) is administered in conjugation with levodopa.
  - **Adverse effects:**
    - *CNS:* nausea, vomiting and hallucinations.
    - *CVS (cardiovascular system):* orthostatic hypotension
    - *Motor complications:* on-off phenomenon at trough (controlled with CR preparations) and dyskinesia (occurring when levodopa is reaching its peak concentration).
  - **Drug interactions:**
    - Vitamine B6 is increasing peripheral decarboxylation of levodopa to dopamine → resulting in failure of the therapy.
    - Tricyclic antidepressents and anticholinergics prolong gastric emptying time and increase decarboxylation in the gut.
- Food which is rich in neutral amino acids interferes with the transport of L-DOPA across the blood-brain barrier.
- Anti-psychotic drugs (neuroleptics) and metoclopramide (used for vomiting) block dopaminergic receptors.

- After years of treating Parkinson’s disease using the precursor replacement strategy → there will be failure of DOPA-therapy → so you have to administer dopamine agonists:
  ✓ Which are classified to:
    ✓ **Ergolines**:
      - Bromocriptine (D2 receptor). It is also used for the treatment of hyperprolactenemia.
      - Pergolide (D1 + D2 receptors).
    ✓ **Non-ergolines (these are mainly used nowadays)**:
      - Pramipexole (D3 receptor).
      - Ropinirole (D2 receptor). It has less side effects than pramipexole.
  ✓ Adverse effects:
    ✓ Nausea and vomiting.
    ✓ Orthostatic hypotension.
    ✓ Hallucinations and psychosis.

- Administarting monoamine oxidase-B (MAO-B) or catechol-o-methyltransferase (COMT) inhibitors to prevent degredation of dopamine (this strategy is not effective as DOPA-therapy).
  ✓ **MAO-B inhibitor (selegiline)**:
    ✓ **Adverse effects**:
      - Serotonin syndrome: due to interaction with pethidine and SSRI antidepressants.
      - Dyskinesia: due to interaction with levodopa.
      - Insomnia and vivid dreams: due to metabolites such as amphetamines.
  ✓ **COMT inhibitors: (entacapone and tolcapone)**:
    ✓ **Adverse effects**:
      - Increasing levodopa-induced dyskinesia.
      - Dry mouth, urine discoloration and iron chelation in gut.

- **Anticholinergics (blocking muscarinic receptors)**:
  - **Examples include**:
    ✓ Orphenadrine (important)
    ✓ Benztropine.
    ✓ Trihexyphenidyl.
    ✓ Procyclidine.
  - **Mainly used in treating tremors and extrapyramidal problems occurring in patients treated with antipsychotics.**
  - **Adverse effects**:
    ✓ CNS: memory impairment and confusion.
    ✓ Autonomic: glaucoma and urinary retention.

- **Antihistamines (diphenhydramine which is belonging to the 1st generation)**:
  - **Mechanism of action**: central anticholinergic effect.
  - **Adverse effects**: sedation.

- **NMDA receptor antagonists (amantadine: it is an antiviral drug)**:
  - **Useful for controlling bradykinesia.**
  - **Adverse effects**:
    ✓ CNS: confusion, hallucination, insomnia, nightmares, dizziness and nausea.
    ✓ CVS: orthostatic hypotension.
- Note that memantine is an approved drug nowadays for the treatment of slow dementia (which is occurring in severe forms of Parkinson’s disease).
- β-blockers (nadolol and propranolol) are used mainly for controlling intention tremor and tremor associated with anxiety.
- Atypical antipsychotics (clozapine and quetiapine) are used to treat hallucination.
- Iatrogenic parkinsonism is caused by:
  - Neuroleptics (typical antipsychotics).
  - Methyldopa: which is used to treat hypertension in pregnancy.
  - Metoclopramide.
  - Reserpine.
- Fava beans are a good natural source to extract levodopa from.