- **Biogenic theories of schizophrenia:**
  - **Dopamine hypothesis:** it states that there is excessive dopamine in the brain (mesolimbic system) → resulting in (+) symptoms of schizophrenia. In contrast, there is deficiency of dopamine in mesocortical system → resulting in (-) symptoms of schizophrenia.
    - Most conventional antipsychotics are D<sub>2</sub>-receptor blockers while atypical antipsychotics have less effects on D<sub>2</sub>-receptors.
    - Amphetamine: enhancing the release of more dopamine from storage vesicles → producing psychosis.
    - Postmortem studies and PET-scan: it was shown that there is increase in dopamine and dopamine receptor in those with schizophrenia.
  - **Serotonin hypothesis:** this hypothesis was based on the following findings:
    - 5HT<sub>2A</sub> agonists (such as LSD “producing vivid visual hallucination” and mescaline) mimic psychotic symptoms of schizophrenia.
    - 5HT<sub>2A</sub> antagonists (such as clozapine and quetiapine) exert antipsychotic effect.
  - **Glutamate hypothesis:** this hypothesis was based on the following findings:
    - NMDA receptor agonists (such as phencyclidine which is producing hallucination) produce cognitive impairment and psychosis.
    - Glutamate receptor agonist may be effective in schizophrenia.
    - Ampakine are effective in animal models of schizophrenia (+ depression) and may act through (BDNF: Brain Derived Neurotropic Factor).
- **Classification of antipsychotic drugs:** there are three possible approaches for classification:
  - **According to type of neurotransmitter blockade:**
    - Dopamine receptor (D<sub>2</sub>) antagonist.
    - 5HT<sub>2A</sub> dopamine receptor antagonist.
  - **According to clinical response:**
    - Conventional/typical antipsychotic drugs (likely to improve positive symptoms within days with minimal improvement in negative symptoms “not before 3-4 months!”).
    - Atypical antipsychotic drugs (likely to improve both positive and negative symptoms of schizophrenia). Why are they not used instead of typical antipsychotics?
      - Because although they improve positive symptoms but not in an effective way as typical antipsychotics do.
      - The benefit of atypical antipsychotics is not immediate (within days).
    - According to onset of response:
      - Rapid onset: the drug which is used in emergency cases is haloperidole (typical antipsychotic) → administered orally/IM → effect after 30 minutes.
      - Gradual (slow) onset.
- **Effects of antipsychotics in patients with schizophrenia:**
  - Reduced initiative and interest in environment.
  - Reduced display of emotions/affect.
  - Reduced aggressive and impulsive behavior.
  - Intact intellectual functions.
  - Drowsy but easily arousable.
- **Therapeutic benefits:**
  - When antipsychotic drugs are given to psychotic patients → they become less agitated.
• When given to a withdrawn patient → he becomes more responsive and communicative.
• Controlling hallucinations and delusions.
• Positive symptoms response earlier and better.
• Negative symptoms usually don’t respond or respond poorly with typical antipsychotics (but they have a better response with the use of atypical antipsychotics).

- **Conventional/typical antipsychotics (drugs which you must memorize):**
  • Haloperidole (for emergency: as was mentioned earlier).
  • Chlorpromazine (blocking all neurotransmitters).
  • Flufenazine

- **Atypical antipsychotics (you must memorize the 1st two drugs):**
  • Clozapine.
  • Quetiapine.
  • Risperidone.
  • Olanzapine.

- **Adverse effects of typical antipsychotics:**
  • Extrapyramidal toxicity: iatrogenic Parkinson’s disease might result because antipsychotic drugs will block dopamine also in nigrostriatal pathway.
  • Sedation.
  • Hypotension: due to adrenoceptor blockade.
  • Remember that dopamine is controlling the secretion of prolactin hormone from anterior pituitary gland. When dopamine is blocked, patients will have **massive secretion of prolactin** resulting in:
    ✓ Menstrual irregularities and galactorrhea (in females).
    ✓ Impotence, gynecomastia and galactorrhea (in males).

- **Depot antipsychotic preparations (IM):**
  • Flufenazine enanthate.
  • Flufenazine decanoate.
  • Haloperidol decanoate.
  • Risperidone long-acting injection.

- **Atypical antipsychotics (dimensions):**
  • Pharmacologist: 5HT₂A – D₂ antagonists
  • Prescriber: low extrapyramidal symptoms; good for negative symptoms
  • Drug industry: new and different; better benefit
  • Formulary committee: expensive
  • Pharmacoeconomist: cost-effective