



- 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 anti-psychotics 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 1<sup>st</sup> 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:** 5HT<sub>2A</sub> – D<sub>2</sub> antagonists
  - **Prescriber:** low extrapyramidal symptoms; good for negative symptoms
  - **Drug industry:** new and different; better benefit
  - **Formulary committee:** expensive
  - **Pharmacoeconomist:** cost-effective