PHARMACOLOGY TEAM

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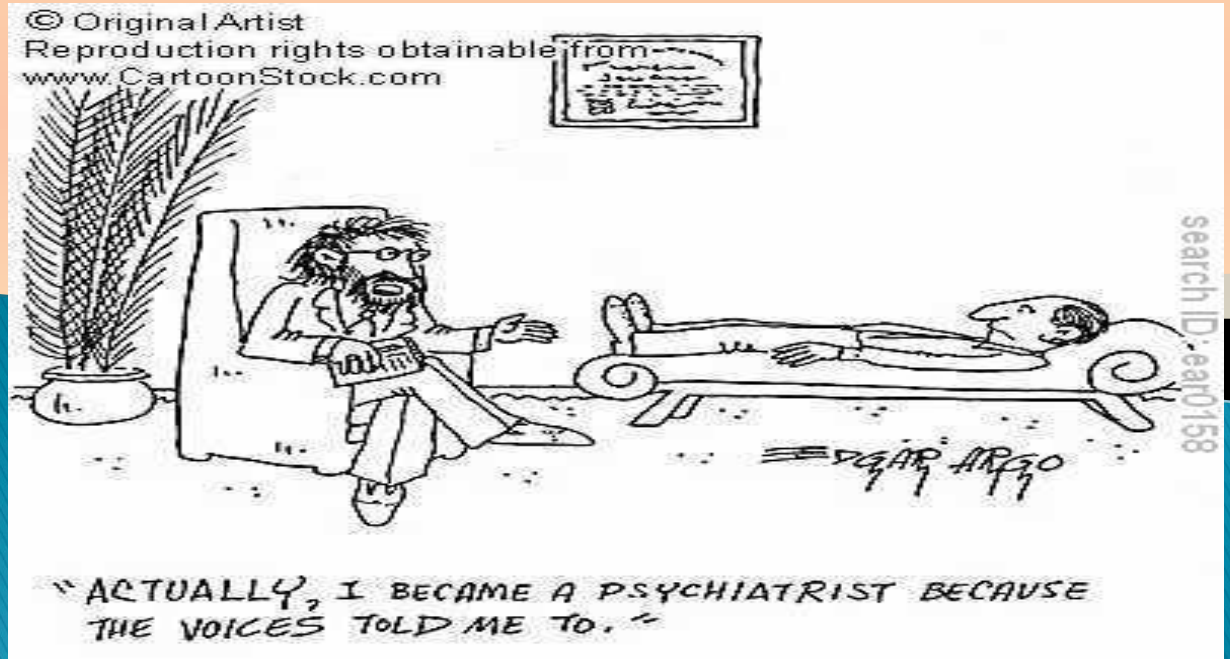
Team note : red color

Drugs used in schizophrenia



Objectives

At the end of the lecture , students should:

- List the classification of antipsychotic drugs used in schizophrenia.
- Describe briefly the mechanism of antipsychotic action of these drugs.
- Describe the pharmacological actions of antipsychotic drugs.
- Relate between pharmacological actions & adverse effects of antipsychotic drugs.

Objectives (con.)

- Enumerate the clinical uses of antipsychotic drugs.

- Describe the advantages of atypical antipsychotic drugs over typical drugs.

Prof.
Abdulrahman
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THE BRAIN IN SCHIZOPHRENIA

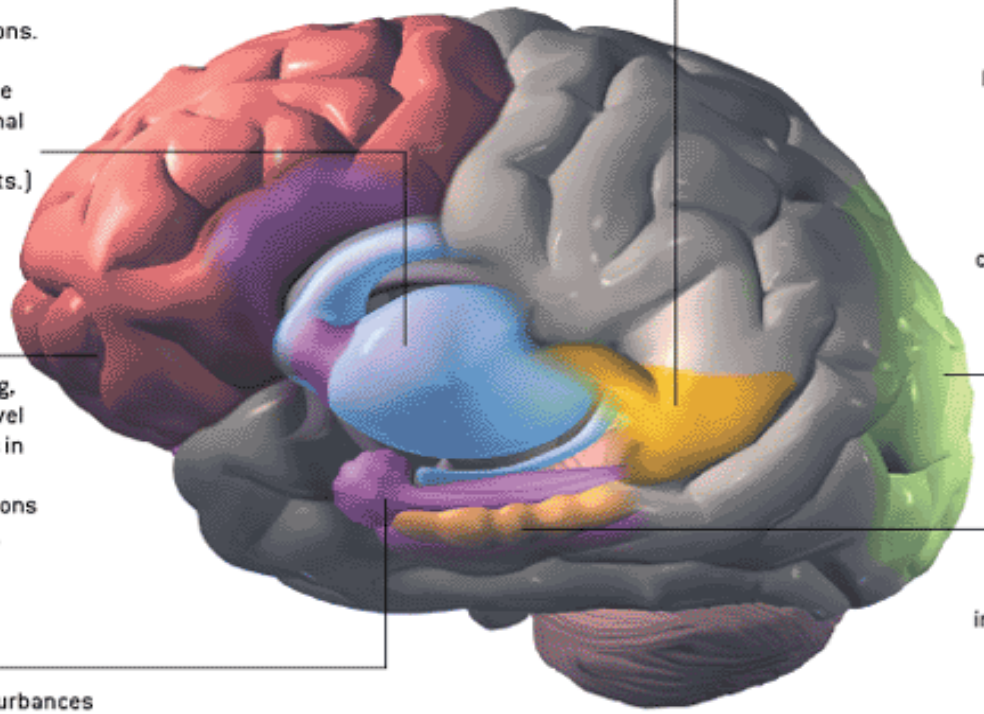
MANY BRAIN REGIONS and systems operate abnormally in schizophrenia, including those highlighted below. Imbalances in the neurotransmitter dopamine were once thought to be the prime cause of schizophrenia. But new findings suggest that impoverished signaling by the more pervasive neurotransmitter glutamate—or, more specifically, by one of glutamate's key targets on neurons (the NMDA receptor)—better explains the wide range of symptoms in this disorder.

BASAL GANGLIA

Involved in movement and emotions and in integrating sensory information. Abnormal functioning in schizophrenia is thought to contribute to paranoia and hallucinations. (Excessive blockade of dopamine receptors in the basal ganglia by traditional antipsychotic medicines leads to motor side effects.)

AUDITORY SYSTEM

Enables humans to hear and understand speech. In schizophrenia, overactivity of the speech area (called Wernicke's area) can create auditory hallucinations—the illusion that internally generated thoughts are real voices coming from the outside.



OCCIPITAL LOBE

Processes information about the visual world. People with schizophrenia rarely have full-blown visual hallucinations, but disturbances in this area contribute to such difficulties as interpreting complex images, recognizing motion, and reading emotions on others' faces.

FRONTAL LOBE

Critical to problem solving, insight and other high-level reasoning. Perturbations in schizophrenia lead to difficulty in planning actions and organizing thoughts.

HIPPOCAMPUS

Mediates learning and memory formation, intertwined functions that are impaired in schizophrenia.

LIMBIC SYSTEM

Involved in emotion. Disturbances are thought to contribute to the agitation frequently seen in schizophrenia.

ALFRED T. KAMAJIAN

Schizophrenia

Positive Symptoms

- Hallucinations (الهلوسة)
- Delusions (أوهام)
- Paranoia

Negative Symptoms

- **Social withdrawal (**lack of contact with people**)**
- **Anhedonia (** absence of pleasure **)**
- **Emotional blunting (** suppression of emotions **)**

Antipsychotic (neuroleptics) drugs

Classification :

Typical Antipsychotic Drugs

According to chemical structure into :

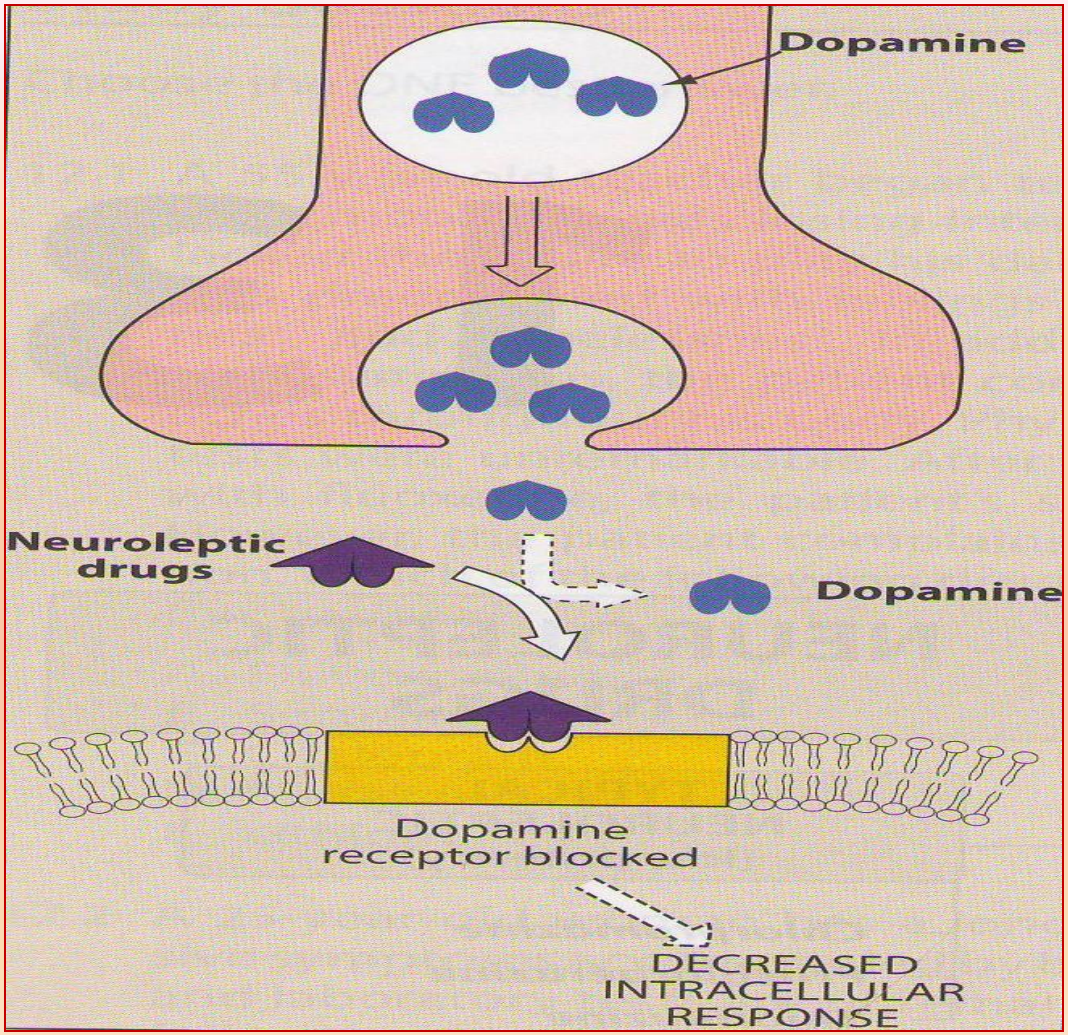
- **Phenothiazine derivatives :**
  - Chlorpromazine
    Thioridazine
- **Butyrophenones**
  - Haloperidol
- **Thioxanthene**
  Thiothixene

Remember, in schizophrenia there's hyperdopmainergic state. So, our aim is to antagonize the dopamine

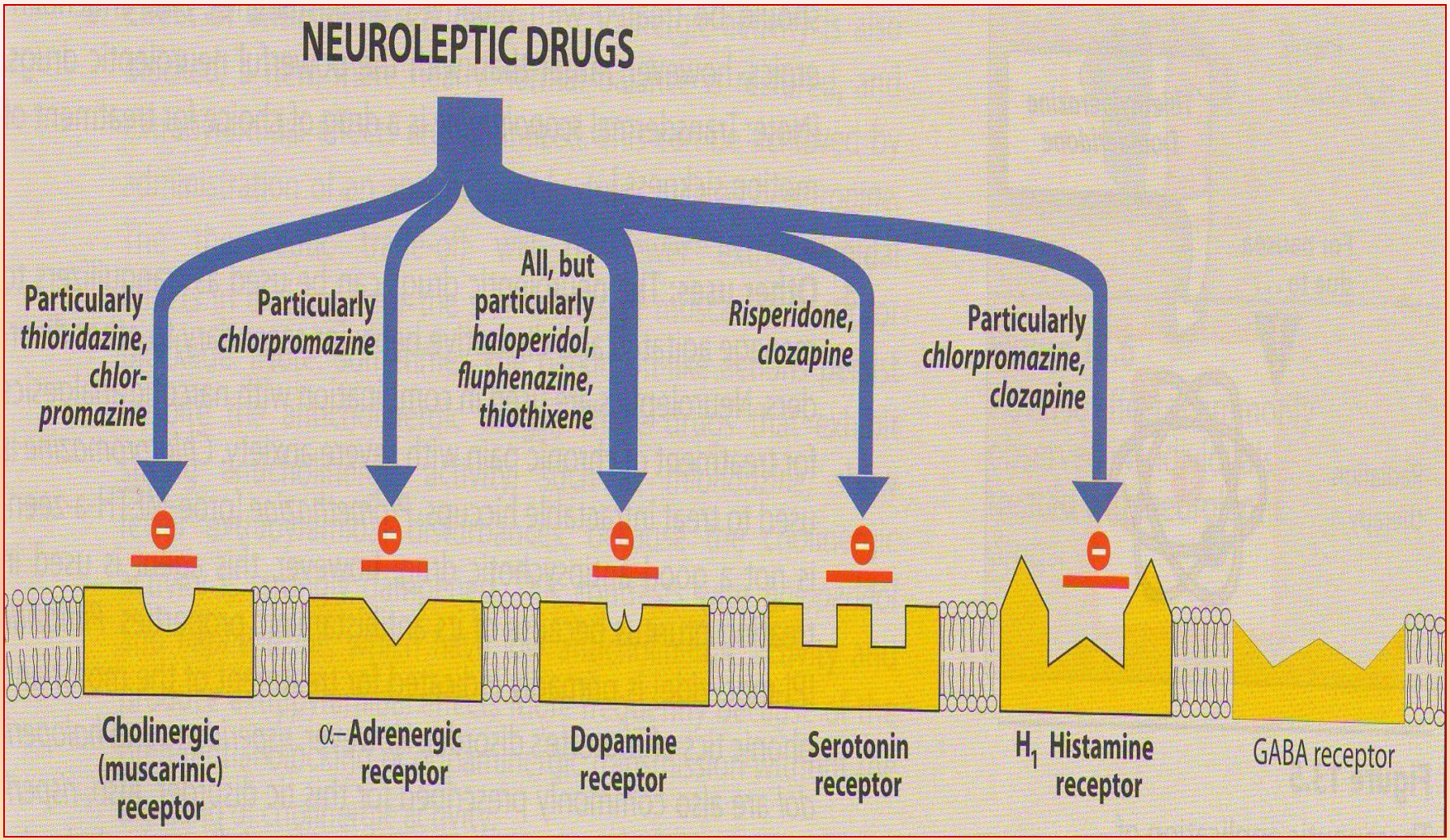
Atypical Antipsychotic Drugs

- Dibenzodiazepines
  - Clozapine
- Benzisoxazoles
  - Risperidone
- Thienobenzodiazepines
  - Olanzapine
- Dibenzothiazepines
  - Quetiapine

Mechanism of Antipsychotic Action



Atypical drugs exert their antipsychotic action through blocking serotonin ($5HT_2$) & dopamine receptors.


NEUROLEPTIC DRUGS
Particularly thioridazine, chlor-promazine
Particularly chlorpromazine
All, but particularly haloperidol, fluphenazine, thiothixene
Risperidone, clozapine
Particularly chlorpromazine, clozapine
Cholinergic (muscarinic) receptor
α–Adrenergic receptor
Dopamine receptor
Serotonin receptor
H1 Histamine receptor
GABA receptor

Pharmacological Actions

C.N.S :

Antipsychotic effect :

- Produce emotional quieting (calming)
- psychomotor (motor effects of cerebral or psychic activity) slowing
- Decreases hallucinations

Mechanism:

Blockade of dopamine receptors in the mesolimbic system.

Pharmacological actions (con.)

Extrapyramidal Symptoms

Abnormal involuntary movements such as tremors, parkinsonism & tardive dyskinesia (involuntary jerky movements)

Mechanism :

Blockade of dopamine receptors in the nigrostriatum system

Endocrine effects

- Galactorrhea (breast milk is produced without childbirth)
- amenorrhea (absence or suppression of normal menstrual)
- gynecomastia (excessive development of the breasts in males)
- impotence
- (hyper prolactinemia).

Mechanism :

Prevent inhibiting effect of dopamine on prolactin release from pituitry (tuberoinfundibular system (one of the four major dopamine pathways in the brain))

Pharmacological Actions (cont.)

Metabolic effects

Changes in eating behavior and weight gain

Mechanism

Blockade of dopamine receptors in the medullary – periventricular pathway

Pharmacological Actions (cont.)

Anti-emetic effect

Effective against drug & disease- induced vomiting (not- motion sickness)

Mechanism :

Blockade of dopamine receptors in the CRTZ

of the medulla

Chemoreceptor Trigger Zone

Pharmacological Actions (con.)

A.N.S

Anticholinergic Effects

- Blurred vision
- Dry mouth
- Urinary retention
- Constipation

Mechanism

Blockade of muscarinic receptors

Continue on A.N.S

Antiadrenergic Effects

- Postural hypotension
- Impotence
- Failure of ejaculation

Mechanism :

Blockade of α- adrenergic receptors

Pharmacological Actions (con.)

Other Actions :

Temperature regulation

Mau cause lowering of body temperature

Mechanism :

Heat loss as a result of vasodilation

(α- blocking)

Or due to central effect

Other Actions (con.)

ECG changes

Prolongation of QT interval

Abnormal configuration of ST- segment & T wave.

Antihistaminic effect

Sedation due to H_1 receptor blockade

Therapeutic USES

PSYCHIATRIC

- Schizophrenia (**primary indication**)
- Acute mania
- Manic-depressive illness)bipolar disorder (

ADVERSE EFFECTS

C.N.S .

Sedation, drowsiness, fatigue

haloperidol , Risperidone

Extrapyramidal symptoms :

Occurring early in the treatment as :

Tremors

occurring late in the treatment as :

After few months as Parkinson,s disease

After several months or years as :

Tardive Dyskinesia &

Neuroleptic Malignant Syndrome

We treat it with anticholinergics to prevent the interaction between other Parkinson`s and antipsychotic drugs.

rare but life threatening condition
muscle rigidity, hyperthermia & coma
due to sudden block of dopamine receptors

Adverse Effects (con.)

A.N.S.

Anticholinergic effects :

Clozapine, Chlorpromazine

Adverse Effects （con)

Antiadrenergic effects :

Chlorpromazine , Thioridazine

Adverse Effects (con.)

Endocrine effects

Adverse Effects (con.)

Miscellaneous Effects :

- Obstrucive jaundice (yellowing of the skin and the whites of the eyes caused by an accumulation of bile pigment in the blood)
- Granular deposits in cornea
- Retinal deposits
- Weight gain

Continue

- Agranulocytosis

  Clozapine (Weekly CBC)

- Seizure

  Clozapine

PHARMACOKINETICS

- Highly lipid soluble → cross BBB & placenta

- Incompletely absorbed
- Highly bound to plasma proteins
- Undergo extensive first-pass hepatic metabolism.

It takes 2-3 weeks for appearing their clinical effects

- Excretion by the kidney

Atypical Antipsychotics

- 2nd Generation antipsychotics
- Are now considered to be first line treatments for schizophrenia
- Little or no extrapyramidal side effects
- Effective in treatment of resistant schizophrenia

- Are effective on both positive & negative symptoms.
- Block both dopaminergic & serotonergic receptors.

CLINICAL USES

- Refractory (not responding to treatment= resistant)cases of schizophrenia.
- To reduce the risk of recurrent suicidal behavior (السلوك الانتحاري) in patients with schizophrenia

CLOZAPINE

Blocks both D_4 & $5HT_2$ receptors

Main adverse effects

- Agranulocytosis
- Seizures (used cautiously in epileptic patients)
- Excessive salivation (during sleep)

RISPERIDONE

- Blocks D_2 & $5HT_2$ receptors

- Main adverse effects
  - –Postural hypotension
  - – QT prolongation
  - – Weight gain

Contraindicated in patients with cardiac problems

OLANZAPINE

- Blocks D_1, D_4 & $5HT_2$ receptors

- Main adverse effects
  - Weight gain
  - Sedation
  - Flatulence (excessive gas in the alimentary canal), increased salivation
  - Postural hypotension
  - Joint stiffness & twitching (وخز)
  - Dental pain & flu syndrome

QUETIAPINE

- Blocks D_1 , D_2 & $5HT_2$ receptors

- Main adverse effects
  - Sedation
  - Hypotension
  - Leukopenia (deficiency in white blood cells) /neutropenia (abnormally low number of neutrophils)
  - hyperglycemia (abnormally high blood sugar)

Summary

- Drugs used in schizophrenia are classified according to chemical structures.

The advantages of atypical drugs includes :

- They block both dopaminergic & serotonergic drugs.
- They are effective in refractory cases of schizophrenia
- They produce few extrapyramidal effects

Summary (con.)

- The pharmacological actions of antipsychotic drugs result from :
- Blocking dopamine receptors at different areas in the brain.
- Blocking antimuscarinic receptors
- Blocking α-adrenergic receptors
- Blocking H1 receptors

Adverse effects are due to:

Blocking dopamine receptors at areas other than mesolimbic area

Summary (con.)

- Blockade H_1, muscarinic & α- adrenergic receptors.
- The main clinical uses is in schizophrenia
- Examples of atypical drugs includes :

  Clozapine

  Risperidone

  Olanzapine

  Quetiapine