

Drugs used in schizophrenia

Objectives

At the end of the lecture , students should be able to :

- 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.

Objectives (con.)

- ▶ Relate between pharmacological actions & adverse effects of antipsychotic drugs.
- ▶ Enumerate the clinical uses of antipsychotic drugs.
- ▶ Describe the advantages of atypical antipsychotic drugs over typical drugs.

Drugs used in the treatment of schizophrenia are called :

Antipsychotic drugs

old name (neuroleptic drugs)

PSYCHOSES

1- Affective Psychoses:

a- Mania

b- Depression

c- Manic-depressive illness
(bipolar affective disorder)

2- Schizophrenia

Schizophrenia

DEFINITION:

- It is a thought disorder characterized by a divorcement from reality in the mind of the patient.
- It may involve hallucinations, delusions, intense suspicion, feelings of persecution or control by external forces (paranoia).

Schizophrenia

Positive Symptoms:

- ▶ **Hallucinations.**
- ▶ **Delusions.**
- ▶ **Paranoia.**

Negative Symptoms:

- ▶ **Social withdrawal.**
- ▶ **Anhedonia (absence of pleasure).**
- ▶ **Emotional blunting.**

Dopamine System

Dopaminergic pathways in the brain :

- 1- Mesolimbic - mesocortical pathway
(behavior)
- 2- Nigrostriatal pathway
(co-ordination of voluntary movements)
- 3- Tuberoinfundibular pathway
(endocrine effects)
- 4- Medullary - periventricular pathway
(metabolic effects)

Dopamine System

Dopamine receptors

There are at least five subtypes of receptors:

D 1, D 2, D 3, D 4, D 5

Antipsychotic drugs

Classification :

According to chemical structure into :
Typical Antipsychotic Drugs:

1-Phenothiazine derivatives

- Chlorpromazine
- Thioridazine

2- Butyrophenones

- Haloperidol

3- Thioxanthene

- Thiothixene

Antipsychotic drugs

Atypical Antipsychotic Drugs :

- ▶ Clozapine.
- ▶ Risperidone.
- ▶ Olanzapine.
- ▶ Quetiapine.
- ▶ Ziprasidone.
- ▶ Cariprazine.

Pharmacological Actions

▶ C.N.S :

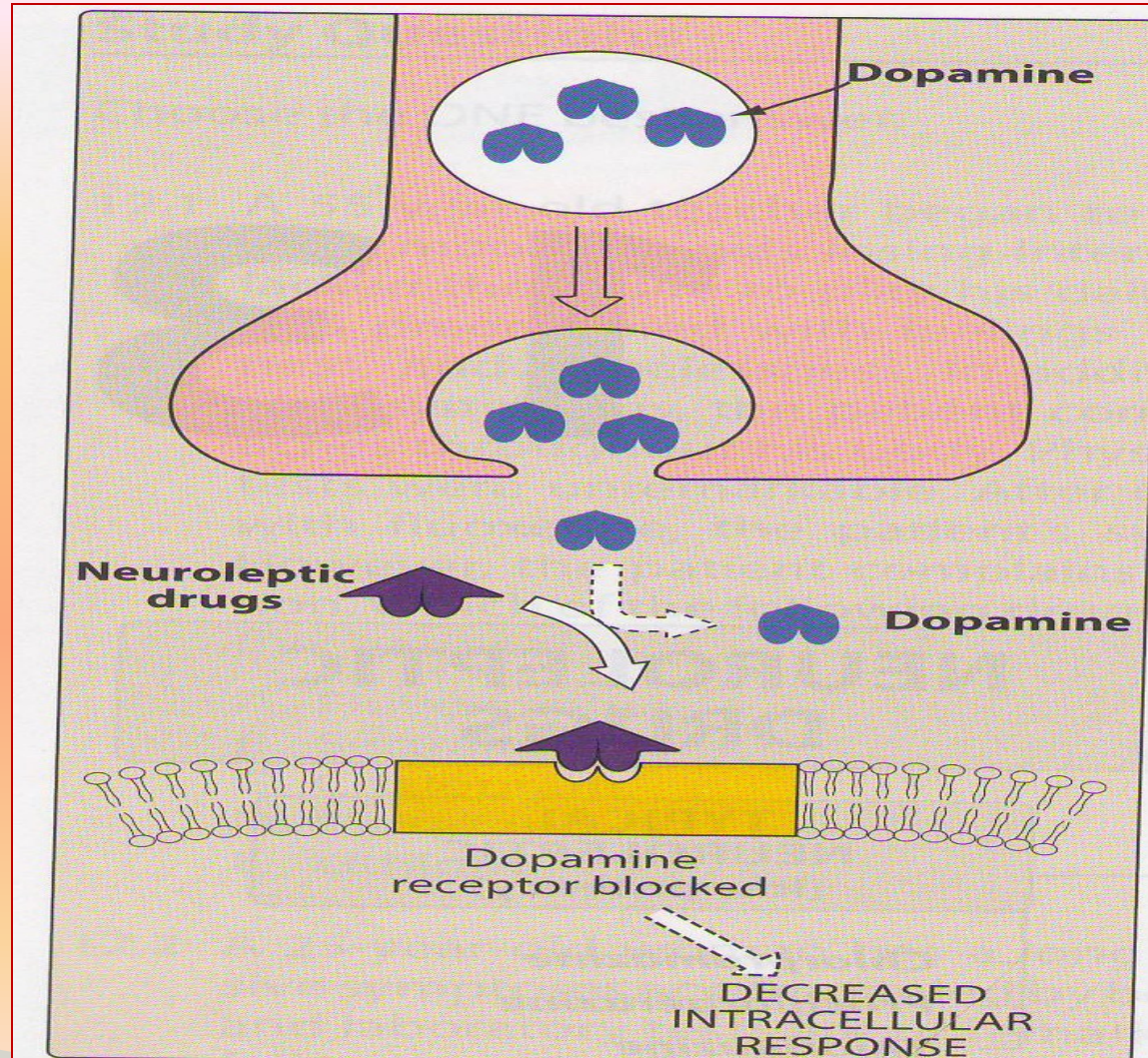
1- Antipsychotic effect :

- ❖ Produce emotional quieting and psychomotor slowing.
- ❖ Decrease hallucinations, delusions and agitation.

Mechanism:

- ❖ Blockade of dopamine receptors in the mesolimbic system.

Mechanism of Antipsychotic Action



- ▶ **Atypical drugs exert their antipsychotic action through blocking serotonergic (5HT₂) & dopaminergic receptors.**

Pharmacological actions (con.)

2- Extrapyramidal Symptoms:

Abnormal involuntary movements such as tremors, parkinsonism & tardive dyskinesia.

Mechanism :

Blockade of dopamine receptors in the nigrostriatum

Pharmacological actions (con.)

3- Endocrine effects

Galactorrhea, amenorrhea, gynecomastia & impotence.

Mechanism :

Prevent dopamine inhibition of prolactin release from pituitary → Hyperprolactinemia

Pharmacological actions (con.)

4- Metabolic effects :

Changes in eating behavior and weight gain.

Mechanism :

Blockade of dopamine receptors in the medullary
– periventricular pathway

Pharmacological actions (con.)

5- Anti-emetic effect :

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

Mechanism :

Blockade of dopamine receptors in the CTZ of the medulla

Pharmacological actions (con.)

A.N.S

1- Anticholinergic Effects :

- Blurred vision.
- Dry mouth.
- Urinary retention.
- Constipation.

Mechanism

Blockade of muscarinic receptors

Pharmacological actions (con.)

2- Antiadrenergic Effects :

- Postural hypotension.
- Impotence.
- Failure of ejaculation.

Mechanism :

Blockade of α - adrenergic receptors

Pharmacological actions (con.)

Other Actions:

1- Temperature regulation :

May cause lowering of body temperature.

Mechanism :

Heat loss as a result of vasodilation
(α - blocking) Or due to central effect.

Pharmacological actions (con.)

2- ECG changes :

Prolongation of QT interval

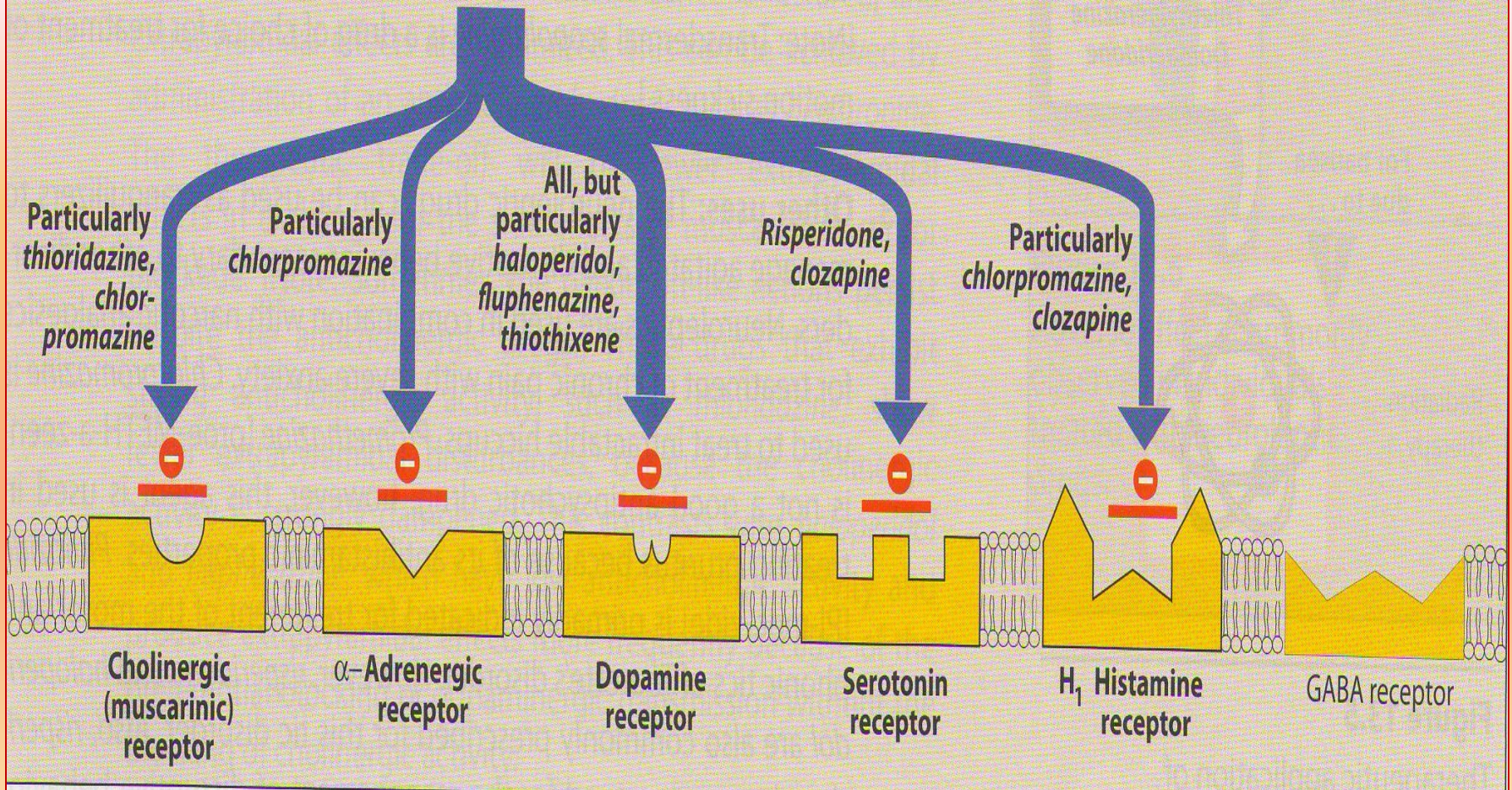
Abnormal configuration of ST- segment & T wave.

3- Antihistaminic effect :

Sedation due to H1 receptor blockade

4- Quinidine –like actions

NEUROLEPTIC DRUGS



Therapeutic Uses

PSYCHIATRIC :

- ▶ **Schizophrenia** (primary indication)
- ▶ **Acute mania**
- ▶ **Manic-depressive illness** (bipolar affective disorder) **during the manic phase**

Therapeutic Uses

NON-PSYCHIATRIC:

1- Nausea and vomiting

- prochlorperazine and benzquinamide are only used as antiemetics

2- Pruritis

3- Preoperative sedation (rare use)

ADVERSE EFFECTS

C.N.S

1- Sedation, drowsiness, fatigue

(haloperidol , Risperidone)

2- Extrapyramidal symptoms :

Some occurring early in treatment as :

Parkinson's syndrome

ADVERSE EFFECTS

Other Extrapyramidal Symptoms are late – occurring :

1- Tardive Dyskinesia (from Latin tardus, slow or late coming)

- ▶ it is a disorder of involuntary movements (choreoathetoid movements of lips, tongue, face, jaws, and limbs)
- ▶ Choreoathetosis : combination of chorea (irregular migrating contractions) and athetosis (twisting)

ADVERSE EFFECTS

2- Neuroleptic Malignant Syndrome

- ▶ Rare but life threatening.
- ▶ Symptoms are muscle rigidity and high fever (clinically similar to anaesthetic malignant hyperthermia).
- ▶ The stress leukocytosis and high fever associated with this syndrome may wrongly suggest an infection.

ADVERSE EFFECTS

A.N.S.

1- Anticholinergic Effects :

- Blurred vision
- Dry mouth
- Urinary retention
- Constipation

(Chlorpromazine , Clozapine)

ADVERSE EFFECTS

2- Antiadrenergic Effects :

- Postural hypotension
 - Impotence
 - Failure of ejaculation
- (**Chlopromazine , Thioridazine**)

ADVERSE EFFECTS

Endocrine Effects :

- Gynecomastia
- Galactorrhoea
- Amenorrhoea

ADVERSE EFFECTS

Miscellaneous Effects :

- Obstrucive jaundice
- Granular deposits in cornea
- Retinal deposits (**thioridazine**)
- Weight gain

ADVERSE EFFECTS

- **Agranulocytosis**

- ▶ **(Clozapine)** about 1-2%
- ▶ usually happen after 6-18 weeks
- ▶ Weekly WBC is mandatory

- **Seizures**

- ▶ **(Clozapine)**

PHARMACOKINETICS

- ▶ **Incompletely absorbed**
- ▶ **Highly lipid soluble**
- ▶ **Highly bound to plasma proteins**
- ▶ **Undergo extensive first-pass hepatic metabolism.**
- ▶ **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 cases of schizophrenia.**
- ▶ **To reduce the risk of recurrent suicidal behavior in patients with schizophrenia**

CLOZAPINE

Blocks both D₄ & 5HT₂ receptors

Main adverse effects

Agranulocytosis

Seizures

Myocarditis

Excessive salivation (during sleep)

RISPERIDONE

- ▶ Blocks D₂ & 5HT₂ receptors

- ▶ **Main adverse effects**

- Postural hypotension.

- QT prolongation.

- Weight gain.

Contraindicated in patients with long QT interval

OLANZAPINE

- ▶ Blocks D₁- D₄ & 5HT₂ receptors
- ▶ **Main adverse effects**
 - Weight gain
 - Sedation
 - Flatulence , increased salivation & thirst
 - Postural hypotension

QUETIAPINE

- ▶ Blocks D₁-D₂ & 5HT₂ receptors
- ▶ **Main adverse effects**
 - Sedation
 - Hypotension
 - Sluggishness
 - Dry mouth

QUETIAPINE

- ▶ **adverse effects (continued..)**
 - Increased appetite (weight gain)
 - Abdominal pain
 - Constipation

Ziprasidone

- Blocks D2 & 5HT2 receptors

Main adverse effects

- Drowsiness
- Akathisia
- Headache
- Dizziness
- Weight gain

Ziprasidone

Drug interactions

- should not be used with any drug that prolongs the QT interval.
- Activity decreased by carbamazepine (inducer of CYP3A4)
- Activity increased by ketoconazole (inhibitor of CYP3A4)

Ziprasidone

WARNING

INCREASE MORTALITY IN ELDERLY PATIENTS

DEMENTIA-RELATED PSYCHOSIS

Cariprazine

- approved in 2015 by the FDA
- has higher affinity at D3 receptor
- has a positive impact on the cognitive symptoms of schizophrenia

Summary

- ▶ Drugs used in schizophrenia are classified according to chemical structures.
- ▶ **The advantages of atypical drugs include :**
- ▶ They block both dopaminergic & serotonergic drugs.
- ▶ They are effective in refractory cases of schizophrenia
- ▶ They produce few extrapyramidal effects

Summary

- ▶ The pharmacological actions of antipsychotic drugs result from :
 - ▶ Blocking dopamine receptors at different areas in the brain.
 - ▶ Blocking muscarinic receptors
 - ▶ Blocking α -adrenergic receptors
 - ▶ Blocking H1 receptors
- ▶ Adverse effects on CNS are due to blocking dopamine receptors at areas other than mesolimbic area

Summary

- ▶ Blockade of H1, muscarinic & α -adrenergic receptors.
- ▶ The main clinical use is in schizophrenia
- ▶ Examples of atypical drugs includes :
 - Clozapine
 - Risperidone
 - Olanzapine
 - Quetiapine
 - Ziprasidone