

Drugs used in schizophrenia

By

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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

- 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:

- **Mania**
- **Depression**
- **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 :**
 - **Mesolimbic - mesocortical pathway**
(behavior)
 - **Nigrostriatal pathway**
(co-ordination of voluntary movements)
 - **Tuberoinfundibular pathway**
(endocrine effects)
 - **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 Classification:

- **Atypical Antipsychotic Drugs:**
 - Clozapine
 - Risperidone
 - Olanzapine
 - Quetiapine
 - Ziprasidone
 - Cariprazine

Pharmacological Actions

- **C.N.S.:**

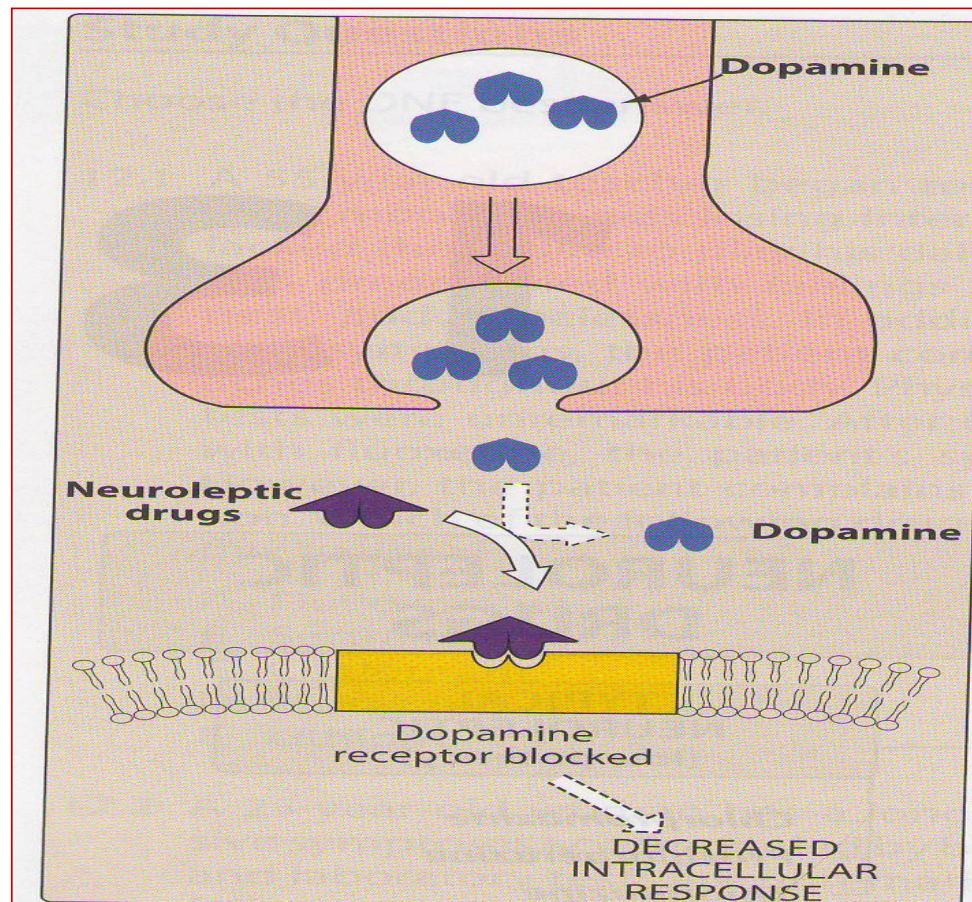
- Antipsychotic effect :

- 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) receptors
- Dopaminergic receptors.

Pharmacological actions (cont.)

Extrapyramidal Symptoms:

- **Abnormal involuntary movements such as:**
 - Tremors
 - Parkinsonism
 - Tardive dyskinesia

Mechanism:

- **Blockade of dopamine receptors in the nigrostriatum**

Pharmacological actions (cont.)

Endocrine effects

- Galactorrhea, amenorrhea, gynecomastia & impotence.

Mechanism:

- Prevent dopamine inhibition of prolactin release from pituitary →
Hyperprolactinemia

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 CTZ of the medulla

Pharmacological actions (cont.)

- **A.N.S**

Anticholinergic Effects:

- Blurred vision
- Dry mouth
- Urinary retention
- Constipation

Mechanism

- Blockade of muscarinic receptors

Pharmacological actions (cont.)

Antiadrenergic Effects:

- Postural hypotension
- Impotence
- Failure of ejaculation

Mechanism:

- Blockade of α - adrenergic receptors

Pharmacological actions (cont.)

Other Actions:

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 (cont.)

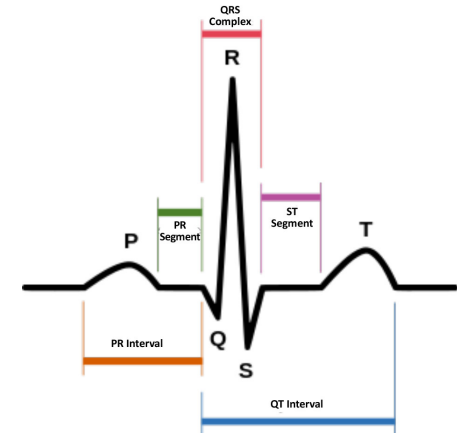
ECG changes:

- Prolongation of QT interval
- Abnormal configuration of ST- segment & T wave.

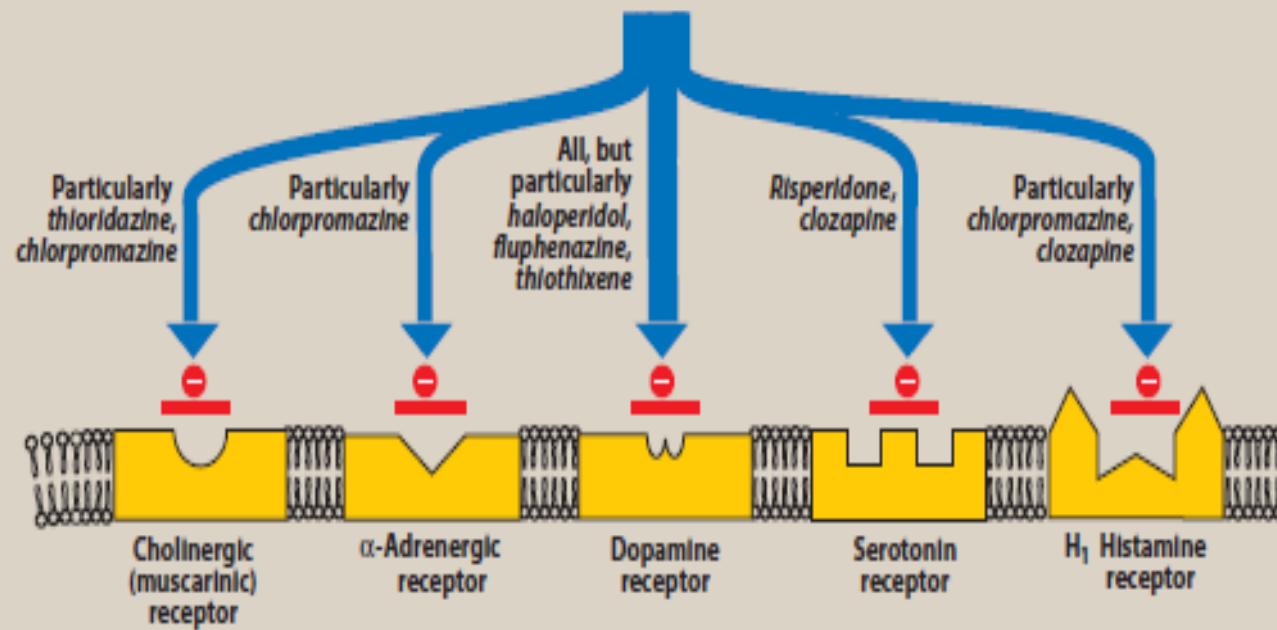
Antihistaminic effect:

- Sedation due to H1 receptor blockade

Quinidine –like actions



ANTIPSYCHOTIC DRUGS



Therapeutic Uses

Psychiatric:

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

Therapeutic Uses

Non-psychiatric:

- **Nausea and vomiting**
 - prochlorperazine and benzquinamide are only used as antiemetics
- **Pruritis**
- **Preoperative sedation (rare use)**

ADVERSE EFFECTS

C.N.S.

- **Sedation, drowsiness, fatigue**
(haloperidol , Risperidone)
- **Extrapyramidal symptoms:**
Some occurring early in treatment as:
Parkinson's syndrome

ADVERSE EFFECTS

Other Extrapyramidal Symptoms are late-occurring:

- **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 and athetosis ; is a movement disorder characterized with irregular migrating contractions

ADVERSE EFFECTS

Neuroleptic Malignant Syndrome

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

ADVERSE EFFECTS

A.N.S.

Anticholinergic Effects:

- Blurred vision
- Dry mouth
- Urinary retention
- Constipation

(Chlorpromazine , Clozapine)

ADVERSE EFFECTS

Antiadrenergic Effects:

- Postural hypotension
- Impotence
- Failure of ejaculation

(**Chlopromazine , Thioridazine**)

ADVERSE EFFECTS

Endocrine Effects:

- Gynecomastia
- Galactorrhoea
- Amenorrhoea

ADVERSE EFFECTS

Miscellaneous Effects:

- Obstructive 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**

Atypical Antipsychotics

- **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**
 - **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



Questions ???

10/28/20