pharmacology
Team 438

MED438
KING SAUD UNIVERSITY

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Neuropsychiatry Block

Pharmacology Team 438

# Drugs Used in Schizophrenia

## Objectives

**By the end of the lecture , you should know:**

- 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
- Enumerate the clinical uses of antipsychotic drugs
- Describe the advantages of atypical antipsychotic drugs over typical drugs

**Color index:**

Black : Main content
Red : Important
Blue: Males' slides only
Pink : Females' slides only
Grey: Extra info or explanation
Green : Dr. notes

Editing File

# Types of Psychoses:

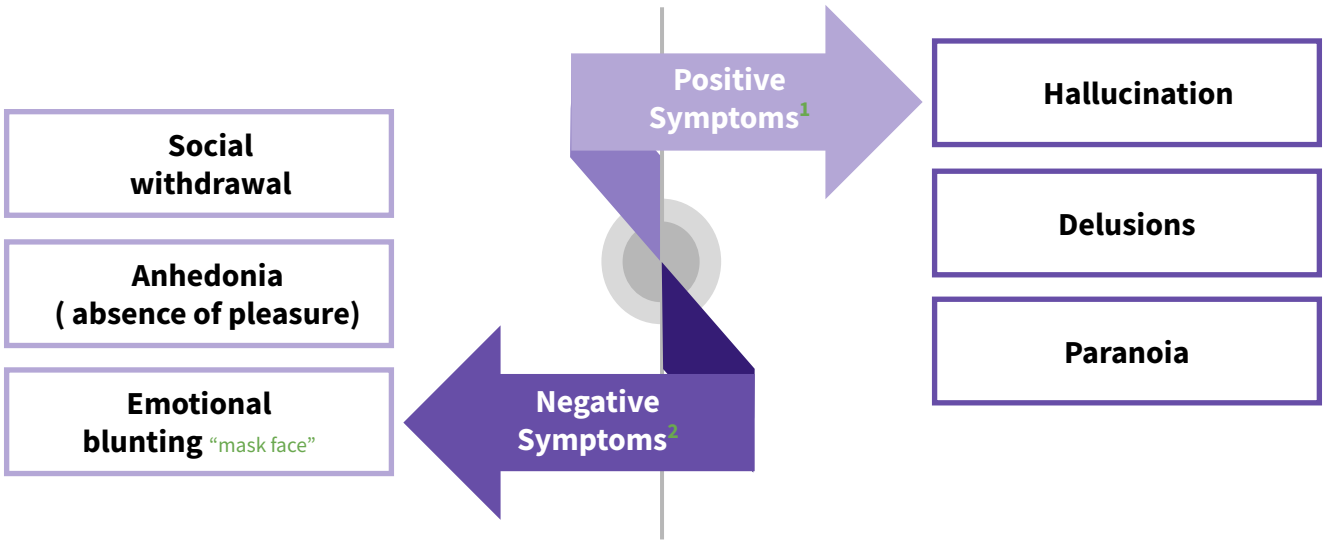
## 1 Affective Psychoses

1) **Mania**
2) **Depression**
3) **Manic-depressive disorder (bipolar)**

## 2 Schizophrenia

- It is a thought disorder characterized by a divorcement from reality in the mind of the patient
- It may involve delusions, hallucinations & paranoia, intense suspicion, feeling of persecution.

# Symptoms of Schizophrenia




# Dopamine System

**Dopamine have 5 receptors in the brain (D1-D5).** It is released in different locations to do different functions. For example, dopamine released at the tuberoinfundibular pathway in the pituitary gland can control the release of prolactin. If this pathway is blocked using any antipsychotic drug, there'll be an increase in prolactin level.

| | |
|---|---|
| Mesolimbic/Mesocortical pathways | Behavioral role |
| Nigrostriatal pathway | Coordination of voluntary movement |
| Tuberoinfundibular pathway | Endocrine effects |
| Periventricular/medullary pathway | Metabolic effects |

1-Positive symptoms are symptoms that are present but should be absent (pathological) and are caused mainly by dopamine irregularity (Ex: Hallucinations and delusions)
2- Negative symptoms are symptoms that reflect absence of normal behavior and are related to serotonin irregular release (Ex: social withdrawal and poverty of speech)

# Types of Antipsychotic drugs

They are classified according to the chemical structure into:

## Typical

"primary, First generation "

- Discovered **first**
- **Nonselective**
- Treat positive symptoms
- **Many** side effects
- Rarely used now
- **Block dopamine receptors**
- works at D2 receptor

## Atypical

" second generation "

- Discovered **later**
- **More** selective
- Treat both positive/negative symptoms
- **Less** side effects
- 1st line of treatment
- **Block dopamine and serotonin receptors**

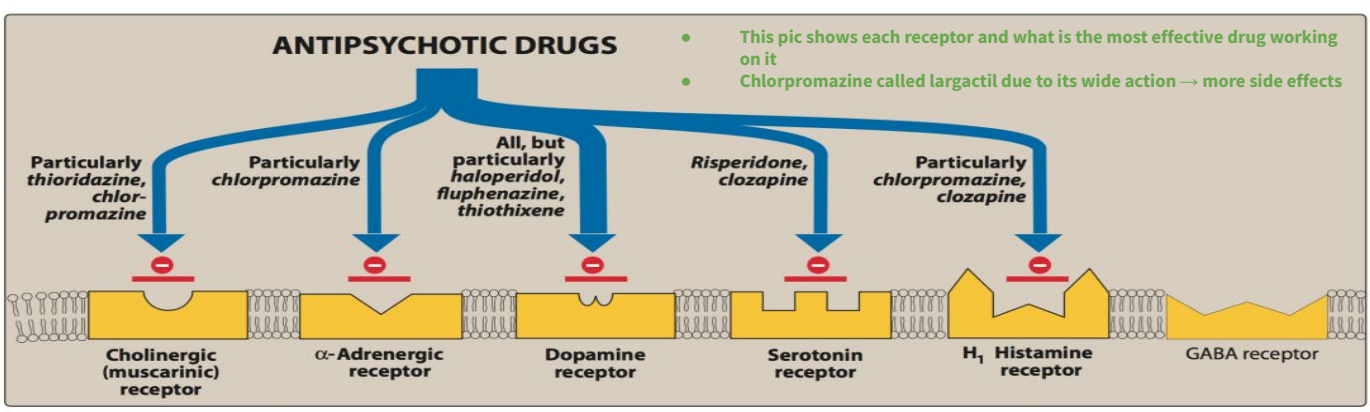
| Class | Class | Drug |
|---|---|---|
| Typical[1] | Phenothiazine<br>Cheating Thieves | **Chlorpromazine**"pro type", **Thioridazine** |
| | Butyrophenones | **Haloperidol** |
| | Thioxanthene | **Thiothixene** |
| Atypical[2] | Dibenzodiazepines | **Clozapine** |
| | Benzisoxazoles | **Risperidone** |
| | Thienobenzodiazepine | **Olanzapine** |
| | Dibenzothiazepines | **Quetiapine** |
| | Benzisothiazoles | **Ziprasidone** |
| | Piperazine/Piperidine? | **Cariprazine** |

# Pharmacological Action

**Antipsychotic drugs acts by blocking receptors. It works by:**

- Blocking dopamine receptors at different pathways [3] (Desired effect)
- Blocking Serotonin receptors (Desired effect)
- Blocking muscarinic receptors
- Blocking a-adrenergic receptors
- Blocking H1 receptors

**Typical drugs work by blocking dopamine receptors (highly selective). While atypical drugs work by blocking both dopamine and serotonin receptors thus it's less selective on dopamine receptors and produces less side effects**




1- you should know the chemical structure and the name of drugs eg: Phenothiazine and its derivatives Chlorpromazine, Thioridazine ,
2-in the Atypical generation knows only the names of drugs
3-These drugs inhibit dopamine pathways due to the high level of dopamine in schizophrenia
4-"Remember to drink some water you beautiful but dehydrated nerd" -lecture reviewer lol

# Pharmacological Action

| Action | Effect | Mechanism |
|---|---|---|
| CNS | **Antipsychotic:**<br>• Produce emotional quieting and psychomotor slowing<br>• Decrease hallucinations, delusions and agitation | Blockage of dopamine receptors in mesolimbic system [1] |
| | **Extrapyramidal symptoms:**<br>• Abnormal movement such as tremors, parkinsonism & Tardive dyskinesia | Blockage of dopamine receptors in nigrostriatal system |
| | **Endocrine:**<br>• Galactorrhea (excessive milk production)<br>• Amenorrhea (abnormal menstruation)<br>• Gynecomastia(enlarged breasts)<br>• Impotence | Prevent dopamine inhibition of prolactin release from pituitary [2] → hyperprolactinemia |
| | **Metabolic:**<br>• Changes in eating behavior and weight gain | Blockage of dopamine receptors in periventricular (medullary) system<br>Decrease in metabolism |
| | **Antiemetic effect [3]:**<br>• Effective against drug and disease-induced vomiting **(not motion sickness)** | Blockage of dopamine receptors in the CTZ of the medulla |
| ANS | **Anticholinergic effect:** " eg : Thiothixene"<br>• Blurred vision<br>• Dry mouth<br>• Urinary retention<br>• Constipation | Blockage of muscarinic receptors |
| | **Antiadrenergic effect:**<br>• Postural hypotension<br>• Impotence<br>• Failure of ejaculation | Blockage of a-adrenergic receptors |
| Other | **Temperature regulation:**<br>• May decrease body temperature [4] | Heat loss as a result of vasodilatation (a-blocking) **OR** due to central effect<br>"Heat center" |
| | **ECG changes**<br>• Prolongation of QT interval " change the rhythm of the heart"<br>• Abnormal configuration of ST-segment and T wave | |
| | **Antihistamine effect:**<br>• Sedation due to H1 receptor blockade | |
| | **Quinidine-like actions** (Block Na channels, antiarrhythmic effect) | |

1- the Favorable pathway , otherwise we consider other pathways as side effects of first generation drugs
2 -Dopamine restrains prolactin production , so when the drugs inhibit dopamine receptors → less dopamine release → hyperprolactinemia
3- eg : chemotherapy drugs
4- Major operations: open heart surgery → to decrease oxygen demands of the heart, eg : Chlorpromazine

# Therapeutic Uses

## 1 Psychiatric

- **Schizophrenia** (main use)
- **Acute mania**
- **Manic-depressive illness** (during manic phase) [1]

## 2 Non-psychiatric

Not important

- **Nausea & vomiting**
  - prochlorperazine and benzquinamide are only used as antiemetics [2]
- **Pruritus**
- **Preoperative sedation** (rarely use)

# Adverse Effects

## CNS

| (1) Sedation, drowsiness, fatigue | **Haloperidol** (typical), **Risperidone** (atypical) |
|---|---|

### (2) Extrapyramidal symptoms

| Early | Late | |
|---|---|---|
| • Occurs early in treatment<br>• Such as: Parkinson's syndrome | **Tardive Dyskinesia** [3]<br>It is a disorder of involuntary movements<br>• Choreoathetoid movements of lips, tongue, face, jaws, and limbs.<br>Choreoathetosis: combination of chorea (irregular migrating contractions) and athetosis (twisting) | **Neuroleptic Malignant syndrome**<br>• Rare but life threatening.<br>• Marked by muscle rigidity and high fever<br>• This syndrome may wrongly suggest an infection due to stress leukocytosis and high fever |

## ANS

| (1) Anticholinergic Effects | (2) Antiadrenergic Effects |
|---|---|
| - Blurred vision<br>- Dry mouth<br>- Urinary retention<br>- Constipation<br>**Chlorpromazine** (typical), **Clozapine** (atypical) | - Postural hypotension<br>- Impotence<br>- Failure of ejaculation<br>**Chlopromazine** (typical), **Thioridazine** (typical) |

## Endocrine Effects [4]

- Gynecomastia
- Galactorrhoea
- Amenorrhoea

## Miscellaneous Effects [5]

- Obstructive Jaundice [6]
- Weight gain
- Retinal deposits (**thioridazine**) [7]
- Granular corneal deposits
- Agranulocytosis (**clozapine**)
- Seizures(**clozapine**)

1- act as mood stabilizers or anti mania drugs
2-Generally , they are antipsychotic drugs but also they have powerful antiemetic effect " eg: cancer chemotherapy"
3- it's irreversible so we should stop the treatment
4- block D2 receptor in the pituitary → hyperprolactinemia
5- Mainly in Chlorpromazine
6- Phenothiazine
7- leads to loss of vision

# Atypical Antipsychotics

## Pharmacokinetics

- Incomplete absorption
- Highly lipid soluble
- Highly bound to proteins
- Excessive first-pass hepatic metabolism
- Excreted by the kidney

## Characteristics

- Second generation
- considered 1st line of treatment of schizophrenia
- Little or no extrapyramidal side effects
- Treats +ve and -ve symptoms
- Blocks both receptors dopaminergic & serotonergic

## Clinical Uses

- Refractory cases of schizophrenia
- Reduce risk of recurrent suicidal behavior in patients with schizophrenia

| Drug | Receptor Blockage | Main ADRs |
|---|---|---|
| **Clozapine** | **$D_4$ and $5HT_2$** | • Agranulocytosis " patient became susceptible to infections "<br>• Seizures<br>• Myocarditis " due to antiarrhythmic effect"<br>• Excessive salivation during sleep |
| **Olanzapine** | **$D_1$ - $D_4$ and $5HT_2$** | • Postural hypotension<br>• Weight gain (**O**besity)<br>• Sedation<br>• Flatulence, thirst & increased salivation |
| **Quetiapine** | **$D_1$ - $D_2$ and $5HT_2$** | • Sedation<br>• Hypotension<br>• Sluggishness<br>• Dry mouth<br>• ↑ appetite (weight gain)<br>• Abdominal pain<br>• Constipation |
| **Cariprazine** | • Approved in 2015 by the FDA<br>• Has higher affinity at D3 receptor<br>• Has positive impact on the cognitive symptoms of schizophrenia (good for dementia) | |
| **Risperidone** | **$D_2$ and $5HT_2$** | • Postural hypotension<br>• Weight gain (**O**besity)<br>• QT prolongation **(contraindicated in cardiac patient with QT prolongation )** |
| **Ziprasidone** [2] | **$D_2$ and $5HT_2$** | • Dizziness & drowsiness<br>• Akathisia (agitation)<br>• Headache<br>• Weight gain (**O**besity) |

### Drug interactions

- **Shouldn't** be used **with** any drug that **prolongs QT interval**
- Activity decreased by carbamazepine (CYP3A4 inducer)
- Activity increased by ketoconazole (CYP3A4 inhibitor)

**WARNING!!**

Increased mortality in elderly with dementia-related psychosis

**1- Which of the following drugs can help in the treatment of Emotional blunting and anhedonia ? Choose Atypical drug**

2- ziprasidone metabolized by CYP 3A4

3- carbamazepine will increase metabolism of ziprasidone thus will decrease activity of the drug

- All therapeutic effect from block of dopamine and serotonin receptors in mesolimbic area others considered as side effect except antiemetic affect .

# Quiz

## MCQ

1- A 53-year-old man with long-standing schizophrenia has failed therapy with both first- and second- Generation antipsychotic agents. He still has significant problems with mood, delusions, and hallucinations. He is placed on clozapine. Which of the following effects must the treating physician be aware of?

A- Choleithiasis B- Polycythemia C- QT prolongation D- Agranulocytosis

2- A 45-year-old man prescribed antipsychotic drugs came to the ER complaining of dizziness when waking up from bed and palpitations. ECG was done and showed prolonged QT interval and disturbed ST segment. Which one of the following drugs was most likely prescribed?

A- Clozapine B- Thioridazine C- Risperidone D- Quetiapine

3- A 53-year-old man with schizophrenia presents to his primary care physician for follow-up. He has been treated with multiple different antipsychotic agents during his lifetime. Which of the following antipsychotic agents has the highest affinity for the D3 receptors?

A- Cariprazine B- Ziprasidone C- Olanzapine D- Quetiapine

4- A 28 year-old lady was diagnosed by schizophrenia. She was prescribed an antipsychotic drug. On further appointments, she started complaining of sudden jerky movements and twisting in her fingers. Aslo, she noticed an increase in her weight without change in her appetite. Which of the following drugs was most likely prescribed

A- Olanzapine B- Risperidone C- Haloperidol D- Clozapine

5- A 33-year-old female is brought to the emergency department by her mother. The patient had a sudden seizure. She also had a very high fever and her temperature upon admission was 40°C (104°F). She has no sick contacts. The mother mentions that she was on a medication for schizophrenia but could not remember the name. A complete blood count shows low neutrophils. Which of the following medications is she likely taking?

A- Chlorpromazine B- Ziprasidone C- Clozapine D- Cariprazine

6- A typical antipsychotic drugs work on all of the following EXCEPT:

A- Dopamine B- Serotonin C- Histamine D- GABA

**MCQ**

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Q1 | D | Q2 | C | Q3 | A | Q4 | C | Q5 | C | Q6 | D |

## *Answers:*

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# *Good Luck , Future Doctors!*

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I love you huqbaniiiii - lecture reviewer

Share with us your ideas !

Don't forget about me guys this great lecture was reviewed by me :(