



## Drugs used in schizophrenia

### Objectives:

- 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:

- Drugs names
- Doctors notes
- Important
- Extra

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# Psychoses



## Schizophrenia

**Definition:** It is a thought disorder characterized by divorcement from reality in mind of patient.

- it may involve hallucinations, delusions, intense suspicion, **feeling of persecution or control by external forces (paranoia)** *Feeling that someone is controlling you (Paranoia).*

**Positive symptoms (Related to dopamine):** 1- hallucinations 2- Delusions 3- paranoia. *Old group (typical) and new group are effective here*

**Negative symptoms (Related to serotonin) :** 1- Social withdrawal 2- Anhedonia (absence of pleasure) 3- Emotional blunting  
*-Old group won't work here, the new group only, also negative symptoms are more difficult to treat.*

## Dopamine system & receptors

### Dopamine pathway in the brain:

1- Mesolimbic-mesocortical pathway

Behavior

2- Nigrostriatal pathway

coordination of voluntary movements

3- Tuberoinfundibular pat

endocrine effects

4- Medullary - periventricular pathway

metabolic effects

### Dopaminergic pathways in the brain:

- There are at least **five** subtypes of Dopamine receptors: D1, D2, D3, D4, D5.

# Antipsychotic drugs overview

- Drugs used in schizophrenia are classified according to chemical structures into:

## Typical

discovered first, **non selective**, many side effects, **rarely** used nowadays.

## Atypical

more selective, less side effects, **1<sup>st</sup>** line treatment for schizophrenia.

## Classification of Antipsychotic

**Typical Antipsychotic Drugs** → affect D2 mainly → treat the +ve symptoms.

|   |                                     |
|---|-------------------------------------|
| Phenothiazine derivatives<br><small>Its chemical structure similar to TCAs → similar ADRs</small> | <b>Chlorpromazine, Thioridazine</b> |
| Butyrophenones  | <b>Haloperidol</b>                  |
| Thioxanthene  | <b>Thiothixene</b>                  |

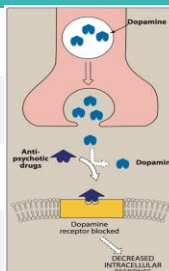
**Atypical Antipsychotic Drugs** → Affect both DA & 5-HT receptors → treat +ve & -ve symptoms.

|                                    |                    |
|------------------------------------|--------------------|
| Dibenzodiazepines*                 | <b>Clozapine</b>   |
| Benzisoxazoles*                    | <b>Risperidone</b> |
| Thienobenzodiazepines*             | <b>Olanzapine</b>  |
| Dibenzothiazepines*                | <b>Quetiapine</b>  |
| Benzisothiazoles*                  | <b>Ziprasidone</b> |
| piperazine/piperidine derivatives* | <b>Cariprazine</b> |

\*Prof. Yieldez said: it's enough to know the drug name only like (Clozapine, Risperidone, ....)

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

They are due to blocking dopamine receptors at areas other than mesolimbic area (**extrapyramidal effects**)

### Advantages of Atypical drugs

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

# Pharmacological actions of typical & atypical anti-psychoses

عشان تكون الصورة واضحة، الـ pharmacological actions تشمل typical & atypical وهي والأعراض الجانبية اللي راح تتذكر بعدها، أهم شي هنا ربط كل أثر مع الـ receptor لأنه بيسهل حفظ الوظائف والأعراض الجانبية مع بعض .

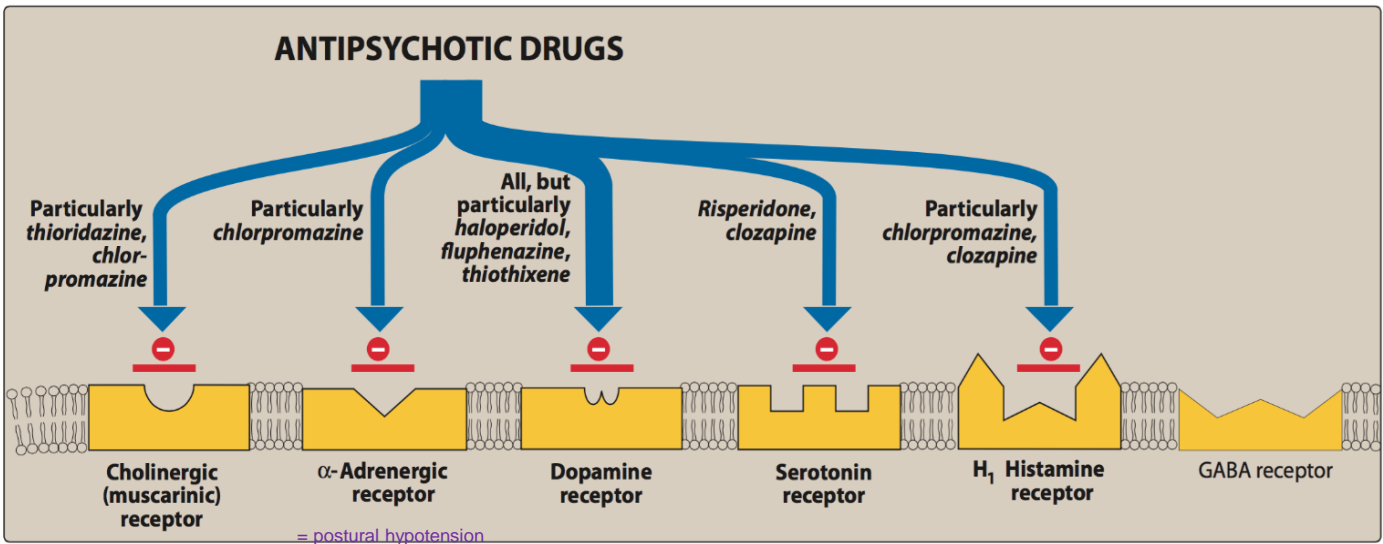
## Before starting the pharmacological actions we need to be familiar with these concepts:

- **Psychomotor slowing:** involves a slowing-down of thought and a reduction of physical movements in an individual.
- **Psychotic disorder:** abnormal thinking and perceptions.
- **Agitation:** a state of anxiety or nervous excitement.
- **Tardive dyskinesia:** a neurological disorder characterized by involuntary movements of the face and jaw.
- **Galactorrhea:** excessive or inappropriate production of milk.
- **Amenorrhea:** an abnormal absence of menstruation.
- **Gynecomastia:** enlargement of a man's breasts, usually due to hormone imbalance or hormone therapy.
- **Impotence:** inability to develop or maintain an erection of the penis during sexual activity in humans.
- **Pruritus:** severe itching of the skin.

| CNS  | ANS  |
|--|--|
| <p><b>Antipsychotic effect:</b> (it's the main use)</p> <ul style="list-style-type: none"> <li>- Produce emotional quieting and psychomotor slowing.</li> <li>- Decreasing hallucinations, delusions and agitation.</li> </ul> <p><b>Mechanism: blockage of dopamine receptors in the mesolimbic system.</b> → treat +ve symptoms.</p> <p><b>Note:</b> Atypical drugs exert their antipsychotic action through <b>blocking serotonergic (5HT<sub>2</sub>) and dopaminergic receptors.</b> → treat -ve symptoms also.</p> | <p><b>Anticholinergic effects:</b></p> <ul style="list-style-type: none"> <li>- Blurred vision</li> <li>- Dry mouth</li> <li>- Urinary retention</li> <li>- Constipation</li> </ul> <p><b>Mechanism: blockage of muscarinic receptors.</b></p> |
| <p><b>Extrapyramidal symptoms:</b></p> <ul style="list-style-type: none"> <li>- Abnormal involuntary movements such as tremors, parkinsonism, and tardive dyskinesia.</li> </ul> <p><b>Mechanism: blockage of dopamine receptors in the nigrostriatum.</b> Ach more than dopamine</p>  | <p><b>Antiadrenergic effects:</b></p> <ul style="list-style-type: none"> <li>- Postural <u>hypotension</u></li> <li>- Impotence</li> <li>- failure of ejaculation.</li> </ul> <p><b>Mechanism: blockage of alpha-adrenergic receptors.</b></p> |
| <p><b>Endocrine effects:</b></p> <ul style="list-style-type: none"> <li>- Galactorrhea</li> <li>- Amenorrhea</li> <li>- Gynecomastia &amp; impotence.</li> </ul> <p><b>Mechanism: prevent dopamine from inhibiting prolactin release from pituitary gland</b> and that will lead to <b>hyperprolactinemia.</b> → نتيجة لقلّة الدوبامين، راح يكثر هرمون البرولاكتين، مما يسبب تأخر الحمل لو ما تعالج.</p>   |  |

# Pharmacological actions Cont.

| CNS   | Other  |
|---|--|
| <p><b>Metabolic effect:</b><br/>- Changes in eating behavior and weight gain.<br/><b>Mechanism: blockage of dopamine receptors in the medullary-periventricular pathway.</b></p>  | <p><b>Temperature regulation:</b><br/>May cause lowering of body temp.<br/><b>Mechanism:</b> heat loss as a result of vasodilation due to alpha-blocking or to central effect. (In major operations; open heart surgery)</p> |
| <p><b>Antiemetic effect:</b><br/>- Effective against drug and disease-induced vomiting. (not-motion sickness)<br/><b>Mechanism: blockage of dopamine receptors in the CTZ</b> of the medulla. The chemoreceptor trigger zone (CTZ) is an area of the medulla oblongata that receives inputs from blood-borne drugs or hormones, and communicates with other structures in the vomiting center to initiate vomiting.</p> | <p><b>ECG changes:</b><br/><b>prolongation of QT interval, abnormal configuration ST segment and T wave.</b><br/>Too prolongation will lead to Torsades de pointes which may lead to ventricular fibrillation</p>            |
|   | <p><b>Antihistaminic effect:</b><br/>sedation due to <b>H1</b> receptor blockage.</p>  |
|   | <p><b>Quinidine-like action</b></p>  |



**Figure 13.4**

Antipsychotic drugs block at dopaminergic and serotonergic receptors as well as at adrenergic, cholinergic, and histamine-binding receptors. GABA =  $\gamma$ -aminobutyric acid.

Chlorpromazine مين أكثر درق ماخذ أغلب الإفكتس؟

# Adverse Effects

نفس الشيء هنا كل الأعراض تشمل typical and atypical مع اختلاف في الدرجة وأغلبهم كانوا مذكورين مع ال pharmacological actions

So most of the pharmacological actions = adverse effects

**Prof. Yildez said: we will ask about the characteristic ADRs of each drug.**

## CNS

1- Sedation, drowsiness, fatigue → (haloperidol (typical) , Risperidone (atypical) )

2- Extrapyrimal symptoms: → Early occurring: Parkinson's syndrome, late occurring:

### A) Tardive Dyskinesia

### B) Neuroleptic Malignant Syndrome

(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)

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.

 Neuroleptic malignant syndrome

## ANS

### 1- Anticholinergic Effects :

### 2- Antiadrenergic Effects :

- Blurred vision
- Dry mouth
- Urinary retention
- Constipation → (Chlorpromazine (typical), Clozapine (atypical))

- Postural hypotension
- Impotence
- Failure of ejaculation (Chlorpromazine (typical), Thioridazine (typical))

## Endocrine Effects

Gynecomastia

Galactorrhoea

Amenorrhoea

# Adverse Effects Cont.

## Miscellaneous Effects \*

\*These ADRs are not related to the drug itself, but related to the genetic susceptibility of person to have these ADRs when he/she take the drugs

**Obstructive jaundice**  
Chlorpromazine

Granular deposits in cornea

**Retinal deposits (thioridazine)**

**Weight gain**

The only one

## Clozapine

### Agranulocytosis

- About 1-2%
- Usually happen after 6-18 weeks
- Weekly WBC is mandatory (increase susceptibility to have infections)
- **Seizures**

Agranulocytosis, also known as agranulosis or granulopenia, is an acute condition involving a severe and dangerous leukopenia (lowered white blood cell count)

# Therapeutic uses

| Psychiatric   | Non-psychiatric   |
|---|---|
| Schizophrenia (primary indication).   | - Nausea and vomiting.<br>→ <b>Prochloroperazine and benzquinamide are <u>only</u> used as antiemetics.</b> |
| Acute mania.  | Pruritus (الحكة)  |
| <b>Manic-depressive illness</b> (bipolar affective disorder) during the <b>manic phase</b> .<br>Bipolar affective disorder is characterized by periods of deep, prolonged, and profound depression that alternate with periods of an excessively elevated or irritable mood known as mania. | Preoperative sedation. ( <b>Rare use</b> )  |

## Pharmacokinetics:

- Incompletely absorbed.
- Highly **lipid soluble**.
- Highly bound to plasma proteins.
- Undergo extensive **first-pass hepatic metabolism**.
- Excretion by the kidney.



How Do Antipsychotic Drugs Work? How Effective are Medications for Schizophrenia & Psychosis?



# Atypical Antipsychotics

- 2<sup>nd</sup> Generation antipsychotics
- **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.

| Risperidone   | Ziprasidone   | Cariprazine   |
|---|---|---|
| <p><b>MOA:</b><br/>Blocks <b>D<sub>2</sub></b> &amp; <b>5HT<sub>2</sub></b> receptors.</p> <p><b>Main adverse effects:</b></p> <ul style="list-style-type: none"> <li>- <b>Postural hypotension</b></li> <li>- <b>QT prolongation</b></li> <li>- Weight gain</li> </ul> <p><b>Contraindicated:</b><br/><b>Patients with long QT interval.</b></p> | <p><b>MOA:</b><br/>Blocks <b>D<sub>2</sub></b> &amp; <b>5HT<sub>2</sub></b> receptors.</p> <p><b>Main adverse effects:</b></p> <ul style="list-style-type: none"> <li>- Drowsiness, <b>Akathisia</b> (cant keep still), Headache, Dizziness, Weight gain.</li> </ul> <p><b>Drug interactions:</b></p> <ul style="list-style-type: none"> <li>- Should <b>not</b> be used with any drug that prolongs the <b>QT</b> interval.</li> <li>- Activity <b>decreased</b> by <b>carbamazepine</b> (inducer of <b>CYP3A4</b>)</li> <li>- Activity <b>increased</b> by <b>ketoconazole</b> (antifungal) (inhibitor of <b>CYP3A4</b>)</li> </ul> <p><b>Important:</b><br/>It increases mortality in elderly patients with <b>dementia-related psychosis</b>.</p> <p style="text-align: center; border: 1px dashed gray; padding: 2px;">Imp to know drug interactions</p> | <ul style="list-style-type: none"> <li>- approved in 2015 by the FDA</li> <li>- <b>has higher affinity at D<sub>3</sub> receptor</b></li> <li>- has a positive impact on the cognitive symptoms of schizophrenia</li> </ul> <div style="border: 1px dashed gray; padding: 5px; margin-top: 10px;"> <p>الدواء هذا مهم مرة أنكم تعرفون على أي دوبامين ريسيبينورز ياتر عليه ، الباقيين مو مرة مهم</p> </div> |

| Clozapine   | Olanzapine  | Quetiapine   |
|---|---|--|
| <p><b>MOA:</b><br/>Blocks both <b>D<sub>4</sub></b> &amp; <b>5HT<sub>2</sub></b> receptors.</p> <p><b>Main adverse effects:</b></p> <ul style="list-style-type: none"> <li>- <b>Agranulocytosis</b></li> <li>- <b>Seizures</b></li> <li>- Myocarditis</li> <li>- Excessive salivation (during sleep)</li> </ul> | <p><b>MOA:</b><br/>Blocks <b>D<sub>1</sub>- D<sub>4</sub></b> &amp; <b>5HT<sub>2</sub></b> receptors.</p> <p><b>Main adverse effects:</b></p> <ul style="list-style-type: none"> <li>- Weight gain</li> <li>- Sedation</li> <li>- Flatulence, <b>increased salivation</b> &amp; thirst.</li> <li>- Postural hypotension.</li> </ul> | <p><b>MOA:</b><br/>Blocks <b>D<sub>1</sub>-D<sub>2</sub></b> &amp; <b>5HT<sub>2</sub></b> receptors.</p> <p><b>Main adverse effects:</b></p> <ul style="list-style-type: none"> <li>- Sedation</li> <li>- Hypotension</li> <li>- <b>Sluggishness</b></li> <li>- Dry mouth</li> <li>- Increased appetite → (weight gain)</li> <li>- Abdominal pain</li> <li>- Constipation</li> </ul> |



# Summary

| Pharmacological Actions | M.O.A   | Effect  | S/E  |
|-------------------------|---|---|--|
| Antipsychotic effect    | Block of DA receptors in the <b>mesolimbic system</b> .   | <ul style="list-style-type: none"> <li>Emotional quieting &amp; psychomotor slowing.</li> <li>hallucinations, delusions and agitation.</li> </ul> | -  |
| Extrapyramidal effect   | Block of DA receptors in the nigrostriatum  | Abnormal involuntary movements  | <ul style="list-style-type: none"> <li><b>Tardive Dyskinesia</b></li> <li>Parkinson's syndrome</li> <li><b>Neuroleptic Malignant Syndrome</b></li> </ul>                           |
| Endocrine effects       | Prevent DA from inhibiting prolactin release from pituitary<br>→ <u>Hyperprolactinemia</u>  | Galactorrhea, Amenorrhea, Gynecomastia & impotence.   |  |
| Metabolic effects       | Blockade of DA receptors in the medullary – periventricular pathway   | Changes in eating behavior and weight gain  | -  |
| Anti-emetic effect      | Blockade of DA receptors in the CTZ of the medulla  | Effective against drug & disease- induced vomiting<br>( <u>NOT motion sickness</u> )  | <b>Prochlorperazine and Benzquinamide are only used as antiemetics</b>   |
| Anticholinergic Effects | Blockade of muscarinic receptors  | <ul style="list-style-type: none"> <li>- Blurred vision</li> <li>- Dry mouth</li> </ul>   | <ul style="list-style-type: none"> <li>- Constipation</li> <li>- Urinary retention</li> </ul> <p><b>Caused mainly by Chlorpromazine , Clozapine</b></p>                            |
| Antiadrenergic Effects  | Blockade of $\alpha$ - adrenergic receptors   | <ul style="list-style-type: none"> <li>- Postural hypotension</li> <li>- Failure of ejaculation</li> </ul>  | <ul style="list-style-type: none"> <li>- Impotence</li> </ul> <p><b>Caused mainly by Chlorpromazine , Thioridazine.</b></p>  |
| Temperature regulation  | Heat loss as a result of vasodilation ( $\alpha$ - blocking )<br>Or due to central effect   | May cause lowering of body temperature  | <b>Uses:</b> in major surgeries like open heart surgery  |
| ECG changes             | <ul style="list-style-type: none"> <li>Prolongation of QT interval</li> <li>Abnormal configuration of ST- segment &amp; T wave. #cardiac patient</li> </ul> |   | <b>Like: Risperidone - Ziprasidone</b>   |
| Antihistaminic effect   | Sedation due to H1 receptor blockade  |   | -  |
| Quinidine –like actions | -   | It causes arrhythmia  | -  |
| Miscellaneous Effects   | -   | -   | <ul style="list-style-type: none"> <li>Obstrucive jaundice.</li> <li>Granular deposits in cornea.</li> <li><b>Retinal deposits (thioridazine)</b></li> <li>Weight gain.</li> </ul> |

# Summary

Atypical Antipsychotics: **acts on both dopaminergic & serotonergic - first line treatment**

| Dose              | Clozapine   | Risperidone   | Olanzapine  | Quetiapine   | Ziprasidone   | Cariprazine        |
|-------------------|---|---|---|--|---|--------------------|
| M.O.A             | Blocks D4 & 5HT2 receptors  | Blocks D2 & 5HT2 receptors  | Blocks D1- D4 & 5HT2 receptors  | Blocks D1- D2 & 5HT2 receptors   | Blocks D2 & 5HT2 receptors  | <b>D3 receptor</b> |
| S/E               | <ul style="list-style-type: none"> <li>● <b>Agranulocytosis</b></li> <li>● <b>Seizures</b></li> <li>● Myocarditis</li> <li>● Excessive salivation (during sleep)</li> </ul> | <ul style="list-style-type: none"> <li>● Postural hypotension</li> <li>● <b>QT prolongation</b></li> <li>● Weight gain</li> <li>● <b>Sedation (also haloperidol)</b></li> </ul> | <ul style="list-style-type: none"> <li>● Weight gain</li> <li>● Sedation</li> <li>● Flatulence, ↑salivation &amp; thirst</li> <li>● Postural hypotension</li> </ul> | <ul style="list-style-type: none"> <li>● Sedation</li> <li>● Hypotension</li> <li>● <u>Sluggishness</u></li> <li>● Dry mouth</li> <li>● Increased appetite (weight gain)</li> <li>● <u>Abdominal pain</u></li> <li>● Constipation</li> </ul> | <ul style="list-style-type: none"> <li>● Drowsiness</li> <li>● <u>Akathisia</u></li> <li>● Headache</li> <li>● Dizziness</li> <li>● Weight gain</li> </ul>  |                    |
| C/I               | -   | in patients with long QT interval cardiac patient   | -   | -  | ↑mortality in elderly patients, with dementia-related psychosis   |                    |
| Drug interactions | -   | -   | -   | -  | <ul style="list-style-type: none"> <li>● should not be used with any drug that <u>prolongs the QT interval.</u></li> <li>● Activity ↓ by <b>carbamazepine</b> (inducer of <b>CYP3A4</b>).</li> <li>● Activity ↑ by <b>ketoconazole</b> (inhibitor of</li> </ul> |                    |

# Questions

## MCQs

Q1/Side effects include anti-cholinergic, anti-adrenergic and extrapyramidal?

- A-haloperidol
- B-lithium
- C-meprobamate
- D-chloral hydrate

Q2/which of the following is the mechanism of action of Clozapine?

- A-Blocks D1-D4 & 5HT2 receptor
- B-Blocks D4 & 5HT2 receptor
- C-Blocks D1-D2 & 5HT2 receptor
- D-Blocks D2 & 5HT2 receptor

Q3/which of the following is an antiemetic effect in the CNS?

- A-sedation due to H1 receptor blockage
- B-Galactorrhea
- C-Effective against drug and disease-induced vomiting. (not-motion sickness)
- D-Blurred vision

Q4/ Which of the following is an advantage of atypical drugs?

- A-they may cause lowering of body temperature
- B-They are not effective in refractory cases of schizophrenia
- C-They block both dopaminergic & serotonergic receptors
- D-They don't produce few extrapyramidal effects

Q5/which of the following drugs can produce constipation?

- A-Risperidone
- B-Thioridazine
- C-Chlorpromazine
- D-haloperidol

MCQs Answers:

- 1-A
- 2-B
- 3-C
- 4-C
- 5-C

# Questions

## MCQs

Q6/which of the following is a positive symptom of Schizophrenia?

- A-Social withdrawal
- B-Delusions
- C-Emotional blunting
- D-Anhedonia (absence of pleasure)

Q7/Which of the following is a atypical antipsychotic drug?

- A-Thiothixene
- B-Thiothixene
- C-Chlorpromazine
- D-Olanzapine

Q8/ which of the following is non-psychiatric therapeutic use?

- A-Acute mania
- B-Schizophrenia (primary indication)
- C-Manic-depressive illness
- D-Pruritus

MCQs Answers:

- 6-B
- 7-D
- 8-D

## SAQ

Q1/A 17 year old male diagnosed with schizophrenia and was treated with haloperidol, can you name three adverse effects for this drug?

Sedation, drowsiness, and fatigue.

Q2/ A 35-year-old man with abnormal behavior has been diagnosed with schizophrenia

A-what is the definition of of schizophrenia?

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

B-Can you name three negative and positive symptoms of schizophrenia?

Positive symptoms :1- hallucinations 2- Delusions 3- paranoia  
Negative symptoms :1- Social withdrawal 2- Anhedonia (absence of pleasure)  
3-Emotional blunting.

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### References:

- Doctors' slides and notes.
- Pharmacology Team 435.

Special thank for team 435 ❤️



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