



## #12

# Drugs used in schizophrenia

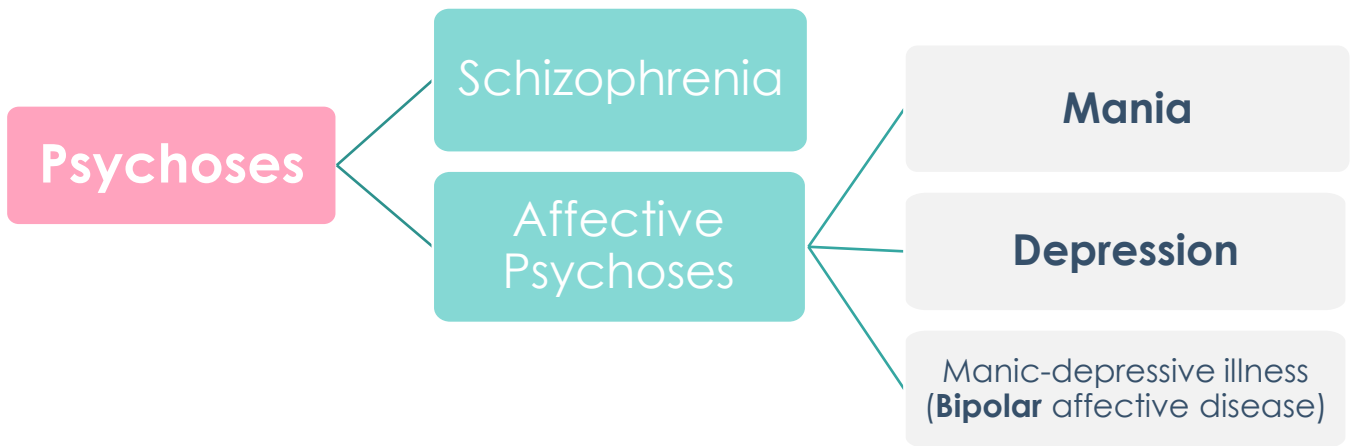
### Objectives:

- 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

# 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).

**Positive symptoms :** 1- hallucinations 2- Delusions 3- paranoia

**Negative symptoms :** 1- Social withdrawal 2- Anhedonia (absence of pleasure) 3-Emotional blunting

## Dopamine system & receptors

### Dopamine pathway in the brain:

1- Mesolimbic-mesocortical pathway

Behavior

2- Nigrostriatal pathway

co-ordination 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.

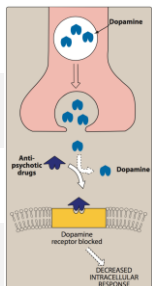
Phenothiazine derivatives <small>Its chemical structure similar to TCAs → similar ADRs</small>	<b>Chlorpromazine, Thioridazine</b>
Butyrophenones	<b>Haloperidol</b>
Thioxanthene	<b>Thiothixene</b>

**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>

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 هي والأعراض الجانبية اللي راح تتذكر بعدها، أهم شي هنا ربط كل أثر مع الـ receptor حقه لأنه بيسهل حفظ الوظائف والأعراض الجانبية مع بعض.

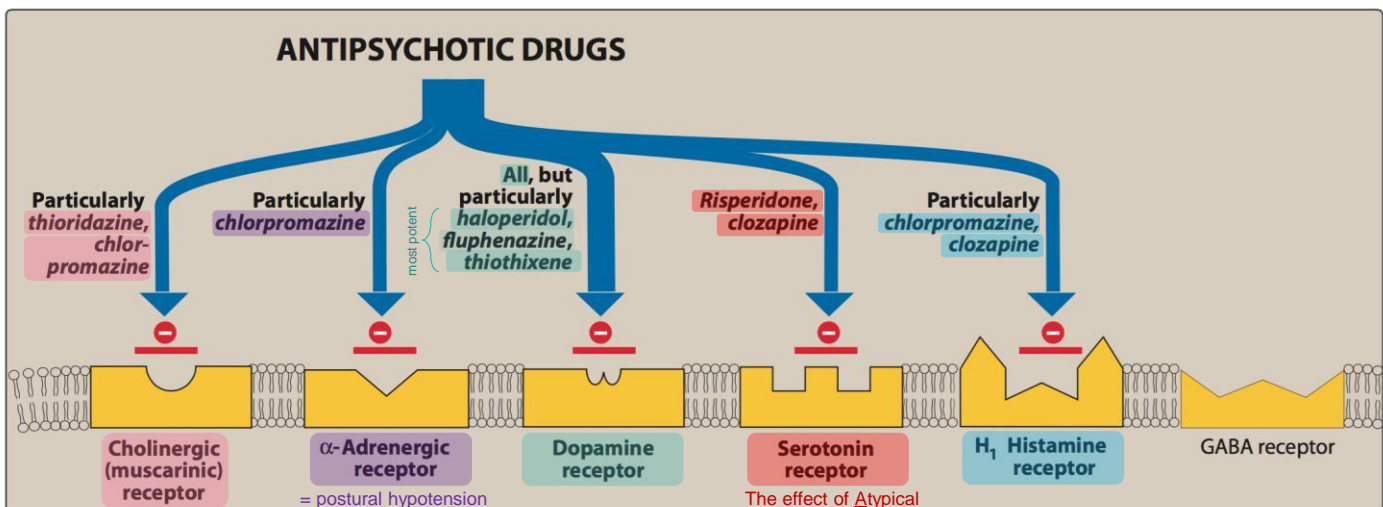
## Before starting the pharmacological actions we need to be familiar with these concepts:

- **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:</b> blockage of <b>dopamine</b> receptors in the <b>mesolimbic</b> system. → 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:</b> blockage of <b>muscarinic</b> receptors.</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:</b> blockage of <b>dopamine</b> receptors in the <b>nigrostriatum</b>.</p>	<p><b>Antiadrenergic effects:</b></p> <ul style="list-style-type: none"> <li>- Postural <u>hypotension</u></li> <li>- Impotence and failure of ejaculation.</li> </ul> <p><b>Mechanism:</b> blockage of <b>alpha 1-adrenergic</b> receptors.</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:</b> prevent <b>dopamine</b> from inhibiting prolactin release from <b>pituitary gland</b> and that will lead to <b>hyperprolactinemia</b>. → نتيجة لقلة الدوبامين، راح يكثر هرمون البرولاكتين، مما يسبب تأخر الحمل لو ما تعالج.</p>	

# Pharmacological actions Cont.

CNS	Other
<p><b>Metabolic effect:</b> - Changes in eating behavior and weight gain. <b>Mechanism:</b> blockage of dopamine receptors in the medullary-periventricular pathway.</p>	<p><b>Temperature regulation:</b> May cause lowering of body temp. <b>Mechanism:</b> heat loss as a result of vasodilation due to alpha1-blocking or central effect.</p>
<p><b>Antiemetic effect:</b> - Effective against drug and disease-induced vomiting. (not-motion sickness) <b>Mechanism:</b> blockage of dopamine receptors in the CTZ 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: prolongation of QT interval, abnormal configuration ST segment and T wave.</b></p>
	<p><b>Antihistaminic effect:</b> sedation due to H1 receptor blockage.</p>
	<p><b>Quinidine-like action:</b> Increasing action potential duration as well as prolonged QT interval.</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.

مين أكثر درق ماخذ أغلب الإفكتس؟ **Chlorpromazine**

هذي الصورة تلخص الإفكتس السابقة وهي المهمة، ديلدز نيهت عليها وطولت في شرحها، مهم جداً تعرفون الدرقر المكتوبة في هذي الصورة وإيش الرستورز اللي تعمل عليها.

# Adverse Effects

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

So most of the pharmacological actions = adverse effects

The drugs mentioned are the **most common for the ADR**

## CNS

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

2- **Extrapyramidal 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

Obstrucive jaundice

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
- 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
<b>Schizophrenia</b> (primary indication).	- Nausea and vomiting. → <b>Prochloroperazine</b> and <b>benzquinamide</b> are <u>only</u> used as <b>antiemetics</b> .
Acute mania.	Pruritus (الحكة)
<b>Manic-depressive illness</b> (bipolar affective disorder) during the <b>manic phase</b> . 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	Clozapine	Olanzapine	Quetiapine
<p><b>MOA:</b> 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>- Postural hypotension</li> <li>- <b>QT prolongation</b></li> <li>- Weight gain</li> </ul> <p><b>Contraindicated:</b> Patients with long <b>QT</b> interval.</p>	<p><b>MOA:</b> 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> It increases mortality in elderly patients with <b>dementia-related psychosis</b>.</p>	<p><b>MOA:</b> 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> 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, increased salivation &amp; thirst.</li> <li>- Postural <u>hypotension</u>.</li> </ul>	<p><b>MOA:</b> 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>- Sluggishness</li> <li>- Dry mouth</li> <li>- Increased appetite → (weight gain)</li> <li>- Abdominal pain</li> <li>- Constipation</li> </ul>



# Summary-1

\* From the doctors' slides.

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

# Summary-2

- Atypical drugs are now **1<sup>st</sup>** line treatment for schizophrenia.
- Effective in treatment of **resistant schizophrenia**.
- Little **or no** extrapyramidal side effects.
- Are effective on both positive & negative symptoms.
- Block **both** dopaminergic & serotonergic receptors.

Drug	ADR	Pharmacological Action	Clinical Uses
<p><b>Clozapine</b></p> <p>Blocks D4&amp; 5HT2 receptors</p>	<ul style="list-style-type: none"> <li>• <b>Agranulocytosis</b></li> <li>• <b>Seizures</b></li> <li>• Myocarditis</li> <li>• Excessive</li> <li>• Salivation (during sleep)</li> </ul>	<p><b>On CNS:</b></p> <ol style="list-style-type: none"> <li>1-anti-sychotic effects</li> <li>2-extrapyramidal</li> <li>3-endocrine effects</li> <li>4-metabolic effects</li> <li>5-anti-emetic effects</li> </ol> <p><b>On ANS:</b></p> <ol style="list-style-type: none"> <li>1-anti-cholinergic effects</li> <li>2-anti-adrenergic effects</li> </ol> <p><b>Other actions:</b></p> <ol style="list-style-type: none"> <li>1-tempreture regulation</li> <li>2-ECG changes</li> <li>3-anti-histamic effects</li> <li>4-QUNIDINE like actions</li> </ol> <p><b>Ziprasidone</b> INCREASE MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA RELATED PSYCHOSIS.</p>	<ul style="list-style-type: none"> <li>• Refractory cases of schizophrenia.</li> <li>• Reduce the risk of recurrent suicidal behavior in patients with schizophrenia</li> </ul>
<p><b>Risperidone</b></p> <p>Blocks D2&amp; 5HT2 receptors</p>	<ul style="list-style-type: none"> <li>• Postural hypotension</li> <li>• Weight gain</li> <li>• <b>QT</b> prolongation</li> <li>• <b>Contraindicated</b> in patients with long QT interval</li> </ul>		
<p><b>Olanzapine</b></p> <p>Blocks D1,D4 &amp; 5HT2 receptors</p>	<ul style="list-style-type: none"> <li>• Weight gain</li> <li>• Sedation</li> <li>• Flatulence</li> <li>• increased salivation</li> <li>• Thirst</li> <li>• Postural hypotension</li> </ul>		
<p><b>Quetiapine</b></p> <p>Blocks D1,D2 &amp; 5HT2 receptors</p>	<ul style="list-style-type: none"> <li>• Sedation</li> <li>• Hypotension</li> <li>• Sluggishness</li> <li>• Dry mouth</li> </ul>		
<p><b>Ziprasidone</b></p> <p>Blocks D2 &amp; 5HT2 receptors</p>	<ul style="list-style-type: none"> <li>• Drowsiness</li> <li>• <b>Akathisia</b></li> <li>• Headache</li> <li>• Dizziness</li> <li>• Weight gain</li> </ul>		

DRUG	THERAPEUTIC NOTES
<b>First generation</b>	
<i>Chlorpromazine</i>	Moderate to high potential for EPS; moderate to high potential for weight gain, orthostasis, sedation, anti-muscarinic effects.
<i>Fluphenazine</i>	Oral formulation has a high potential for EPS; low potential for weight gain, sedation, and orthostasis; low to moderate potential for anti-muscarinic effects; common use is in the LAI formulation administered every 2-3 weeks in patients with schizophrenia and a history of non-compliance with oral antipsychotic regimens.
<i>Haloperidol</i>	High potential for EPS; low potential for anti-adrenergic (orthostasis) or anti-muscarinic adverse events; low potential for weight gain or sedation; available in a LAI formulation administered every 4 weeks.
<b>Second generation</b>	
<i>Aripiprazole</i>	Low potential for EPS; low potential for weight gain; low potential for sedation and anti-muscarinic effects; also approved for the treatment of bipolar disorder; also approved for autistic disorder in children, and as an adjunctive treatment for major depression.
<i>Asenapine</i>	Low potential for EPS; low potential for weight gain; low to moderate potential for sedation; low potential for orthostasis; also approved for the treatment of bipolar disorder; available as a sublingual formulation.
<i>Clozapine</i>	Very low potential for EPS; risk for blood dyscrasias (eg. agranulocytosis = ~1%); risk for seizures; risk for myocarditis; high potential for the following: sialorrhea, weight gain, anti-muscarinic effects, orthostasis, and sedation.
<i>Olanzapine</i>	Low potential for EPS; moderate to high potential for weight gain and sedation; low potential for orthostasis; also approved for the treatment of bipolar disorder; available as a LAI formulation administered every 2-4 weeks.
<i>Paliperidone</i>	Low to moderate potential for EPS; low potential for weight gain; low potential for sedation; available as a LAI formulation administered every 4 weeks; also approved for use in schizo-affective disorder.
<i>Quetiapine</i>	Low potential for EPS; moderate potential for weight gain; moderate potential for orthostasis; moderate to high potential for sedation; also approved for the treatment of bipolar disorder and as an adjunctive treatment for major depression.
<i>Risperidone</i>	Low to moderate potential for EPS; low to moderate potential for weight gain; low to moderate potential for orthostasis; low to moderate potential for sedation; also approved for the treatment of bipolar disorder; also approved for autistic disorder in children; available as a LAI formulation administered every 2 weeks.
<i>Ziprasidone</i>	Low potential for extrapyramidal effects; contraindicated in patients with history of cardiac arrhythmias; minimal weight gain. Used in treatment of bipolar depression.

**Figure 13.8**

Summary of antipsychotic agents commonly used to treat schizophrenia. EPS = extrapyramidal effects; LAI = long-acting injectable.



Thank you for checking our team!



Pharmacology 435

@pharmacology435

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حصه المزيني  
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رغدة قاسم  
ريم العقيل  
سارا الحسين  
ساره الخليفة  
لمى الزامل  
لولوه الصفير  
لينا اسماعيل  
ملاك اليحيى  
نورة البصيص

Sources:

1- 435's lecture

2- Pharmacology (Lippincotts Illustrated Reviews Series), 5th edition

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