

Neuropsychiatry Block

Pharmacology Team 439



Helpful video

Color index:

Main Text

Important

Dr's Notes

Female Slides

Male Slides

Extra

Drugs Used in Schizophrenia

Objectives:

- 1- List the classification of antipsychotic drugs used in schizophrenia.
- 2- Describe briefly the mechanism of antipsychotic action of these drugs.
- 3- Describe the pharmacological actions of antipsychotic drugs.
- 4- Relate between pharmacological actions & adverse effects of antipsychotic drugs.
- 5- Enumerate the clinical uses of antipsychotic drugs.
- 6- Describe the advantages of atypical antipsychotic drugs over typical drugs.

Types of Psychoses

Affective Psychoses

(mood disorders)

- 1- Mania
- 2- Depression
- 3- Manic-depressive disorder (Bipolar affective disorder)

Schizophrenia

Definition: It is a thought disorder characterized by a **divorcement** from reality in the mind of the patient. may involve hallucinations, delusion, Intense suspicion, feeling of persecution or control by external forces (paranoia).

Treatment: **Antipsychotic drugs** (previously named as neuroleptic drugs).

Symptoms of schizophrenia



Positive symptoms

Feelings or behaviors that are usually not present.

Hallucination

Delusions

Paranoia

Negative symptoms

an absence or lack of normal mental function

Social withdrawal

Anhedonia (absence of pleasure)

Emotional blunting "mask face"



The "dopamine hypothesis" of schizophrenia states that symptoms arise because of excessive dopaminergic activity in mesolimbic system. Dopamine agonists cause psychosis. Dopamine antagonists have antipsychotic actions. Serotonin is increasingly seen as a part of the etiology of schizophrenia.

Dopamine System

Dopamine has at least 5 subtypes of receptors in the brain (D_1 - D_5)

Dopaminergic pathways in the brain are:

Mesolimbic/Mesocortical pathway	Behavior
Nigrostriatal pathway	Coordination of voluntary movement
Tuberoinfundibular pathway	Endocrine effects
Periventricular/medullary pathway	Metabolic effects

Types of Antipsychotic drugs

Classified according to their **chemical structure** into

Typical:

- 1- Block dopamine receptor
- 2- Discovered first
- 3- Nonselective
- 4- Many side effect
- 5- Rarely used now
- 6- Treat positive symptoms

Atypical:

- 1- Block dopamine and serotonin receptors
- 2- Discovered later
- 3- More selective
- 4- Treat both positive and negative symptoms
- 5- Less side effects
- 6- 1st line of treatment.

Class	Chemical structure	Drug
Typical	Phenothiazine derivatives	Chlorpromazine, Thioridazine
	Butyrophenones	Haloperidol
	Thioxanthene	Thiothixene
Atypical	Dibenzodiazepines	Clozapine
	Benzisoxazoles	Risperidone
	Thienobenzodiazepine	Olanzapine
	Dibenzothiazepine	Quetiapine
	Benzisothiazoles	Ziprasidone
	Piperazine	Cariprazine

Pharmacological action

Antipsychotic (Atypical) drugs acts by blocking receptors. It works by:-

- Blocking dopamine receptors at different pathway
- Blocking serotonergic (5-HT₂), muscarinic, α-adrenergic and H₁ receptors

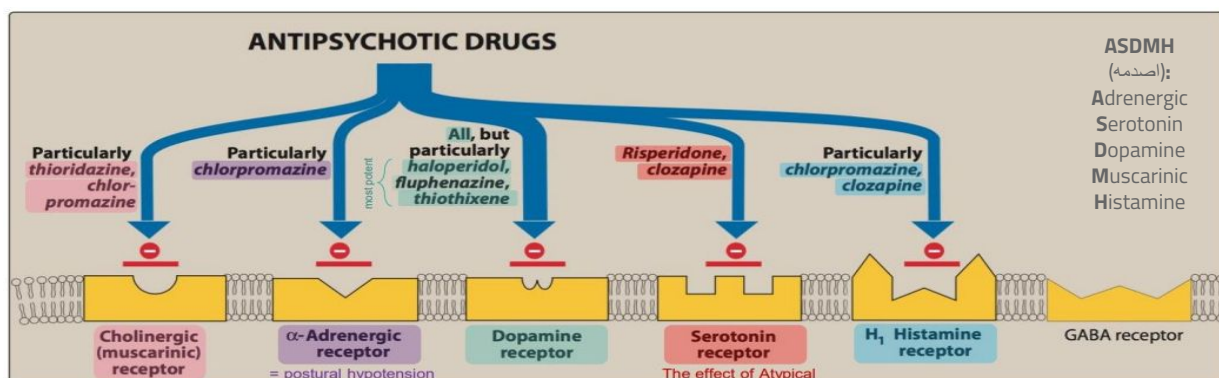
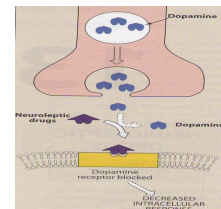


Figure 13.4

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

Pharmacological action

Action	Effect	Mechanism
CNS	Antipsychotic (Major Tranquilizer): <ul style="list-style-type: none"> Produce emotional quieting and psychomotor slowing* Decrease hallucination, delusions and agitation <small>*Psychomotor activity is defined as motor/physical activity that is secondary to or dependent on a psychic component</small>	Blockade of dopamine receptors in mesolimbic system
	Extrapyramidal symptoms: <ul style="list-style-type: none"> Abnormal involuntary movement such as tremors, parkinsonism and Tardive dyskinesia (involuntary movements of the face and jaw) ■ Parkinsonism includes muscle rigidity and loss of movement coordinations 	Blockade of dopamine receptors in nigrostriatum (nigrostriatal system)
	Endocrine: <ul style="list-style-type: none"> Galactorrhea (excessive milk production) Amenorrhea (abnormal menstruation) Gynecomastia (enlarged breasts) Impotence 	Prevent dopamine inhibition of prolactin release From pituitary gland → hyperprolactinemia
	Metabolic: <ul style="list-style-type: none"> Changes in eating behavior and weight gain (<i>bulimia nervosa</i>) 	Blockade of dopamine receptors in the medullary-periventricular pathway
	Antiemetic effect: <ul style="list-style-type: none"> Effective against drug and disease-induced vomiting (not motion sickness) 	Blockade of dopamine receptors in CTZ (Chemoreceptor trigger zone) of the medulla
ANS	Anticholinergic effect: <ul style="list-style-type: none"> Blurred vision Dry mouth Urinary retention Constipation 	Blockade of muscarinic receptors
	Antiadrenergic effect: <ul style="list-style-type: none"> Postural hypotension Impotence Failure of ejaculation 	Blockade of α -adrenergic receptors
Other	Temperature regulation: <ul style="list-style-type: none"> May decrease body temperature ■ Hypothermia: 35° → mild, 32° → moderate, 28° → severe 	Heat loss as a result of vasodilation. (α -blocking) or due to central effect -Blocking of D ₁ and D ₄ leads to failure of regulation in the center of thermoregulation (medulla)
	ECG changes: <ul style="list-style-type: none"> Prolongation of QT interval Abnormal configuration of ST-segment and T wave 	
	Antihistamine effect: <ul style="list-style-type: none"> Sedation due to H₁ receptor blockade 	
	Quinidine-like actions: <ul style="list-style-type: none"> blocking of Na & K Channels. Muscarinic blocking α adrenergic blocking QT prolongation 	

Therapeutic Uses

Psychiatric

- Schizophrenia (primary indication)
- Acute mania
- Manic-Depressive illness (Bipolar Affective disorder) **especially** during the manic phase

Non-Psychiatric

- Nausea & vomiting **Not first line** (prochlorperazine and benzquinamide are only used as antiemetics)
- Pruritus **if there is no pathology** (Psychological itch)
- Preoperative sedation (rarely used)

Adverse Effects

CNS

(1) Sedation, drowsiness, fatigue

Haloperidol (typical), **Risperidone** (atypical)

(2) Extrapyramidal symptoms

Early

Late

- Occurs early in treatment
- Such as: **Parkinson's syndrome**



- 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, **muscle spasms**) and athetosis (twisting, **involuntary movements of face, fingers and limbs**)

2- Neuroleptic Malignant syndrome*



- Rare but life threatening.
- Marked by 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.

*This syndrome can easily be confused with serotonin syndrome so we usually look for lead pipe rigidity. In serotonin you will find Clonus



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

Miscellaneous Effects

▪ Obstructive Jaundice

▪ Weight gain

▪ **Retinal deposits (thioridazine)** Remember drugs working on the eye? Phenothiazine caused deposits

▪ Granular Deposits in cornea

▪ Seizures (**clozapine**) due to blocking of D_4 in the mesolimbic pathway

▪ **Agranulocytosis** is an acute condition involving severe and dangerous neutropenia (**clozapine**):
 - In about 1-2% -Usually happen after 6-18 weeks -Weekly WBC is mandatory

Atypical Antipsychotics

Pharmacokinetics	Characteristics	Clinical Uses
<ul style="list-style-type: none"> Incomplete absorption Highly lipid soluble Highly bound to plasma proteins Extensive first-pass hepatic metabolism Excreted by the kidney 	<ul style="list-style-type: none"> 2nd generation antipsychotics Now considered as 1st line of treatment of schizophrenia Little or no extrapyramidal side effects Effective in treatment of resistant schizophrenia Effective on both +ve and -ve symptoms Blocks both dopaminergic & serotonergic receptors. 	<ul style="list-style-type: none"> Refractory cases of schizophrenia Reduce risk of recurrent suicidal behavior in patients with schizophrenia

Knowing the MoA and the ADRs is very very very important, so this table is important.

★ Drug	Receptor Blockage	Main ADRs
Clozapine	D ₄ and 5-HT ₂	<ul style="list-style-type: none"> Agranulocytosis Seizures Myocarditis Unknown mechanism Excessive salivation during sleep
Olanzapine	D ₁ - D ₄ and 5-HT ₂ <small>D₁ to D₄ so D₂ & D₃ are included</small>	<ul style="list-style-type: none"> Postural hypotension Weight gain (Obesity) Sedation Flatulence, thirst & increased salivation
Quetiapine	D ₁ - D ₂ and 5-HT ₂	<ul style="list-style-type: none"> Sedation by blocking histaminergic receptors Hypotension by blocking α₁ receptor Sluggishness Dry mouth due to anticholinergic effect Increase appetite (weight gain) due to blockade of 5-HT₂ receptors which mediates satiation or feeling of fullness. Abdominal pain Constipation due to anticholinergic effect
Cariprazine		<ul style="list-style-type: none"> Approved in 2015 by the FDA Has higher affinity at D₃ receptor and serotonin Has positive impact on the cognitive symptoms of Schizophrenia
Risperidone	D ₂ and 5-HT ₂	<ul style="list-style-type: none"> Postural hypotension Weight gain (Obesity) QT prolongation (contraindicated in cardiac patient with QT prolongation or patients on QT prolonging drugs)
Ziprasidone	D ₂ and 5-HT ₂	<ul style="list-style-type: none"> Dizziness & Drowsiness Akathisia (restlessness usually in legs) Headache Weight gain (Obesity)
	Drug interactions	
		<ul style="list-style-type: none"> Shouldn't be used with any drug that prolongs QT interval Activity decreased by carbamazepine (CYP3A4 inducer) Activity increased by ketoconazole (CYP3A4 inhibitor) <p style="text-align: center;">WARNING!!!</p> <p>Increased mortality in elderly with dementia-related psychosis due to arrhythmia from QT prolongation <small>Dr. Mohammed: "recent studies suggest that this drug is safe in elderly, so don't be shocked if you heard this in the future"</small></p>



IMPORTANT NOTE:

There are three drugs that specially increase the QT interval; which are: Ziprasidone, Risperidone & Thioridazine.

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

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

Extra info from Kaplan lecture notes

Table IV-4-1. Characteristic Properties of Antipsychotic Drugs

Drug Group Examples	EPS*	M Block	Sedation	Alpha Block	Other Characteristics
Typicals					
Chlorpromazine	++	++	+++	+++	NA
Thioridazine	+	+++	+++	+++	<ul style="list-style-type: none"> • Cardiotoxicity (torsades—"quinidine-like") • Retinal deposits
Fluphenazine	+++	+	+	+	NA
Haloperidol	+++	+	+	+	Most likely cause of neuroleptic malignant syndrome (NMS) and TD
Atypicals					
Clozapine	+/-	++	+	+++	<ul style="list-style-type: none"> • Blocks D_{2c} and 5HT₂ receptors • No TD • Agranulocytosis—(weekly WBC count) requirement for weekly blood test, weight gain • Increased salivation ("wet pillow" syndrome) • Seizures
Olanzapine	+/-	+	+	++	Blocks 5HT ₂ receptors, improves negative-symptoms
Risperidone	+	+/-	++	++	Blocks 5HT ₂ receptors, improves negative symptoms, increased prolactin
Aripiprazole	+	+/-	+/-	+/-	Partial agonist of D ₂ receptor; blocks 5HT ₂ receptors
Other atypicals: quetiapine, ziprasidone					

* Extrapyramidal symptoms

MCQs

Q1: Which antipsychotic agent is most associated with the possibility of a hematological dyscrasia such as agranulocytosis in a patient being treated for schizophrenia?			
A- Chlorpromazine	B-Buspirone	C-Lithium	D-Clozapine
Q2: Which of the following is considered as positive symptoms of Schizophrenia?			
A- Social withdrawal	B-Paranoia	C-Anhedonia	D-Emotional blunting
Q3: The Mesolimbic - mesocortical pathway is responsible for?			
A- Behavior	B-Coordination of voluntary movements	C-Endocrine effects	D-Metabolic effects
Q4: Which drug is classified as a typical antipsychotic?			
A- Cariprazine	B-Ziprasidone	C-Chlorpromazine	D-Clozapine
Q5: Which one of the following drugs cause Akathisia?			
A- Cariprazine	B- Ziprasidone	C- Clozapine	D- Olanzapine
Q6: A 45-year-old male patient with prolonged QT interval and he was diagnosed with schizophrenia, which one of the following drug is contraindicated ?			
A-Quetiapine	B- Cariprazine	C- Risperidone	D- Olanzapine
Q7: A 32-year-old patient came to the clinic complaining of excessive salivation during sleep, and he's using an antipsychotic drug because of schizophrenia, which one of the following drugs caused this problem?			
A- Clozapine	B- Ziprasidone	C- Quetiapine	D-Risperidone
Q8: Which one of the following drugs has higher affinity to D ₃ receptor?			
A- Clozapine	B- Cariprazine	C- Risperidone	D- Ziprasidone
Q9: A 17-year-old man is ready for discharge from the psychiatric ward after stabilisation following an acute episode of schizophrenia. His <u>BP is 135/72 mmHg</u> , <u>pulse is 70/min</u> and regular and his <u>BMI is 27</u> . Accordingly,Which of the following is the most commonly reported side effects of olanzapine therapy ?			
A- Seizures	B- Drowsiness	C- Alopecia	D- Weight gain

1	2	3	4	5	6	7	8	9
D	B	A	C	B	C	A	B	D

SAQ

Q1) What is Neuroleptic malignant syndrome?

Q2) Mention THREE of Ziprasidone drug interactions

Q3) Mention Olanzapine MoA and ADR

Q4) What are the clinical uses of Atypical antipsychotics Drugs?

Q5) What are the Miscellaneous Adverse Effects of Antipsychotics Drugs?

Q6) What are the Psychiatric therapeutic uses of Antipsychotics Drugs?

Answers

A1) Life threatening side effect of antipsychotics (rare). Characterized by muscle rigidity, High fever, and leukocytosis. It can be mistaken for infection

A2) Any drug that prolongs the QT interval, carbamazepine (enzyme inducer), ketoconazole (enzyme inhibitor)

A3) It blocks from D_1 to D_4 & $5-HT_2$ receptors. Its main adverse effects are Weight gain, Sedation, Flatulence, increased salivation & thirst and Postural hypotension

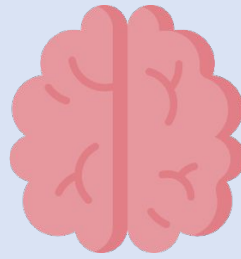
A4) Refractory cases of schizophrenia / Reduce risk of recurrent suicidal behavior in patients with schizophrenia

A5) Obstructive Jaundice/ Weight gain/ Retinal deposits(thioridazine)/ Granular corneal (in cornea) deposits/ Seizures(clozapine)/ Agranulocytosis (clozapine)

A6) Schizophrenia (main use)/ Acute mania Manic/ Depressive illness (Bipolar Affective disorder) during the manic phase



Feedback Form



Neuropsychiatry Block

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