Drugs used in schizophrenia

- Main text
- Male slide
- Female slide
- Important
- Dr, notes
- Extra info

EDITING FILE

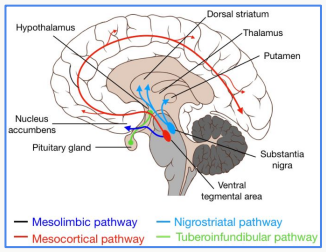
Objectives

- Classify antipsychotic drugs used in schizophrenia.
- Describe briefly the mechanism of action for antipsychotic drugs.
- Describe the pharmacological actions of antipsychotic drugs.
- Correlate 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.

Dopamine System

Dopamine

has at least 5 subtypes of dopamine receptors in the brain (D_1-D_5)
Dopaminergic pathways in the brain are:



Important

Mesolimbic/Mesocortical pathway	Behavior "symptomatic control of schizophrenia"
Nigrostriatal pathway	Coordination of voluntary movement "If receptor is blocked: Parkinson like symptoms"
Tuberoinfundibular pathway	Endocrine effects "hyperprolactinemia"
Periventricular/medullary pathway	Metabolic effects "weight gain"

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.

Types of Psychosis

Affective Psychosis	Schizophrenia
• Mania • Depression • Manic-depressive disorder (Bipolar affective disorder)	**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). • Caused by neurotransmitter imbalances in the brain including serotonin, norepinephrine, and dopamine **Treatment:** Antipsychotic drugs (old name: neuroleptic drugs).

Symptoms of schizophrenia

Positive symptoms

Feelings or behaviors that are not typically present in healthy individuals. Related to Dopamine receptors.

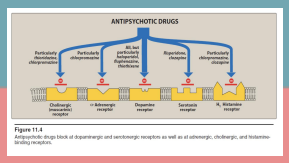
- Hallucination
- Delusions
- Paranoia

Negative symptoms

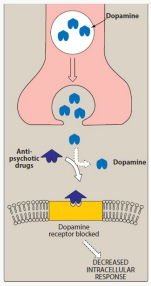
absence or reduction of normal emotions or behaviors that are typically present in healthy individuals. Related to Serotonin receptors.

- Social withdrawal
- Anhedonia (absence of pleasure)
- Emotional blunting

Types of Antipsychotic Drugs



Classified according to their chemical structure into:

Class	Action	★ Drug
Important **Typical** 1st generation	• exert their antipsychotic action via blocking dopaminergic receptors. • MOA: Blocks many receptors including **dopamine,** serotonin, adrenergic, cholinergic, and histaminergic receptors. • Many side effects	<u>Phenothiazine derivatives:</u> • **Chlorpromazine** • **Thioridazine** <u>Butyrophenones</u>: • **Haloperidol** <u>Thioxanthene:</u> • **Thiothixene**
Atypical **(2nd generation)** Used more clinically	• MOA: Block both **dopaminergic** & **serotonergic** (5HT-2) receptors. • Less side effects 	Clozapine Olanzapine Quetiapine Risperidone Ziprasidone Cariprazine

Therapeutic Uses:

Psychiatric	• **Schizophrenia** (primary indication) (overactivity of dopamine in the brain =>Antipsychotic drugs) • Acute mania • Manic-Depressive illness (**Bipolar** Affective disorder) during the manic phase.
Non-Psychiatric	• Nausea & vomiting (prochlorperazine, chlorpromazine and benzquinamide are **only** used as antiemetics) • Pruritus severe itching (Why? because they block Histamine receptors) • Preoperative sedation (rarely used)

Pharmacokinetics:

- Incomplete absorption
- Highly lipid soluble
- Highly bound to plasma proteins
- Undergo extensive first-pass hepatic metabolism
- Excreted by the kidney "should be careful if patient has kidney disfunction"

Wanted Pharmacological actions:

Action on	Mechanism	Effect
CNS	Block Dopamine receptors in: **Mesolimbic system**	**Antipsychotic:** • Produce emotional quieting and psychomotor slowing • Decrease hallucination,delusions and agitation

Unwanted Pharmacological actions (ADRS):

Adverse effects on CNS are due to the blockage of dopamine receptors at areas **other** than the **mesolimbic system**, *What's meant by side effects in this context is related to the treatment of schizophrenia*

Action on	Mechanism	Effect
CNS	Block H1 receptor	**Antihistamine effect:** • Sedation,drowsiness,fatigue **Haloperidol** (typical) **Risperidone** (atypical)
	Block Dopamine receptors in: **Tuberoinfundibular pathway** prevent dopamine inhibition action on prolactin release from pituitary → hyperprolactinemia (Dopamine has a negative feedback action on Prolactin "↓Dopamine→ ↑Prolactin")	**Endocrine:** Male Dr hinted about it but wasn't specific • Galactorrhea (excessive production of milk) • Amenorrhea (missing one or more periods) • Gynecomastia (enlarged breasts in men) • Impotence
	• Block Dopamine receptors in: **Medullary-periventricular pathway** • Mainly by targeting serotonin receptor 2C	**Metabolic:** • Changes in eating behavior and **weight gain (increased the risk of diabetes).**
	Block Dopamine receptors in: **CTZ of the medulla.** (CTZ: chemoreceptor trigger zone)	**Antiemetic** Effective against drug and disease induced vomiting (not motion sickness)
	Block Dopamine receptors in: **Nigrostriatum (nigrostriatal pathway)**	**Extrapyramidal symptoms** *check table below* • Abnormal involuntary movement such as tremors, **parkinsonism like syndrome** and **Tardive dyskinesia**

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) and athetosis (twisting)	**2-Neuroleptic Malignant syndrome** • 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**★★. •Treatment of malignant hyperthermia: **Dantrolene** (muscle relaxant)

Unwanted Pharmacological actions (ADRS):

Action on	Mechanism	Effect
ANS Autonomic Nervous System Mainly caused by typical drugs due to their low sensitivity (affect more receptors), although it can also occur with atypical drugs.	Block **Muscarinic** receptors	**1.Anticholinergic effect:** • Blurred vision • Dry mouth • Urinary retention • Constipation **Chlorpromazine** (typical) **Clozapine** (atypical)
	Block **α-adrenergic** receptors	**2.Antiadrenergic effect:** • Postural hypotension • Impotence • Failure of ejaculation **Chlorpromazine** (typical) **Thioridazine** (typical)

Miscellaneous Effects:

✧**Temperature regulation:** "not common"	Lowering body temperature (MOA): heat loss as a result of vasodilation,due to α-blocking or central effect (hypothalamus).
✧ **ECG changes:**	1. Prolongation of QT interval 2. Abnormal configuration of ST-segment and T wave 3. Quinidine-like actions: blockage of Na & K channels, muscarinic receptors , α adrenergic receptors and QT prolongation
✧ **Obstructive Jaundice**	Caused by ★**Chlorpromazine**
✧ **Weight gain** (blockade of serotonin receptor)	
✧ **Granular Deposits in cornea**	
✧ **Thioridazine:**	**Retinal deposits**
✧ **Clozapine:**	✧ **Seizures** ★**Agranulocytosis** (an acute condition involving severe and dangerous ↓WBC) (high risk of infection). - In about 1-2%. -Usually happen after 6-18 weeks. -Weekly **WBC** is mandatory

Chlorpromazine has lower potency and more severe anticholinergic and adrenergic side effects.

The increased anticholinergic effect of chlorpromazine, however, lowers the risk of extrapyramidal symptoms

Atypical antipsychotics (newer gen)

Characteristics	Clinical Uses
• Now considered as **1st line of treatment of schizophrenia** • Little/no extrapyramidal side effects (an advantage) • Effective in treatment of resistant schizophrenia • Effective on both +ve and -ve symptoms • **Blocks** both **dopaminergic & serotonergic 5HT$_2$** receptors.	• Refractory cases of schizophrenia • Reduce the risk of recurrent suicidal behavior in schizophrenia patients

Drug	Receptor Blockage	Main ADRs
Quetiapine	Blocks D1-D2 & 5HT2 receptors	• **Sedation** due to blockage of histaminergic receptors • **Hypotension** due to blockage of α1 receptor • Sluggishness • Dry mouth & Constipation due to anticholinergic effect • Increase appetite (**weight gain**) due to blockade of 5-HT2 receptors • Abdominal pain
Risperidone	Blocks D2 & 5HT2 receptors	• **Postural hypotension** • **Weight gain** • ★**QT prolongation**: C.I in cardiac patient with QT prolongation •Sedation
Ziprasidone	Blocks D2 & 5HT2 receptors	• Dizziness & Drowsiness • Akathisia • Headache • **Weight gain**
	Drug interactions	
	• Shouldn't be used with any drug that prolongs QT interval (Antiarrhythmic drug) • Activity decreased by carbamazepine (CYP3A4 inducer) • Activity increased by ketoconazole (CYP3A4 inhibitor) **WARNING!! Increased mortality in elderly with dementia-related psychosis**	
Cariprazine	• Approved in 2015 by the FDA • Has higher affinity at **D3** receptor "only one to close D3" • Has positive impact on the **cognitive** symptoms of Schizophrenia (Used in psychotic patients with memory dysfunction)	
Olanzapine ★first line treatment for schizophrenia	Blocks D1-D4 & 5HT2 receptors	• **Postural hypotension** • **Weight gain** • **Sedation** • Flatulence, thirst & increased salivation
Clozapine 1st atypical drug developed	Blocks both D2 / D4 & 5HT2a receptors	• ★**Agranulocytosis** • Seizures • Myocarditis • Excessive salivation during sleep -Multiple case reports have linked **olanzapine** and **clozapine** to new-onset type 2 **diabetes**, and all antipsychotics should be monitored for this ADR

★Summary from girls slides

Advantages of atypical drugs

-Blocks both dopaminergic & serotonergic drugs.

-Effective in refractory cases of schizophrenia

-Few extrapyramidal effects.

Drugs used in schizophrenia are classified according to their chemical structures & the main Clinical use is in schizophrenia

Pharmacological actions of antipsychotic drugs results from blocking of:
-Dopamine receptors, at different areas of the brain.
-Muscarinic receptors.
-α-adrenergic receptors
-H1 receptors
ADRS of the CNS are caused by blocking of dopamine receptors at areas other than the Mesolimbic area

Examples of atypical drugs includes:
Clozapine Risperidone Olanzapine Quetiapine Ziprasidone

Summary from boys slides.

Drugs	Typical Antipsychotics	Atypical Antipsychotics
Examples	Chlorpromazine, Thioridazine, Haloperidol, Thiothixene	Clozapine, Risperidon, Olanzapine, Quetiapine, Ziprasidone, Cariprazine
MOA	Blocks D2 receptors	Block D2 (less) & 5HT2A (more) receptors.
Effects	More effects on positive symptoms	More effects on negative symptoms
Extrapyramidal side effects	Common	Less common
★Neuroleptic Malignant Syndrome	**Common**	**Less common**
★Endocrine Side Effects	**Less common**	**Common**

MCQ

1.Which of the following is considered a 1st-line of treatment for patients with Schizophrenia?			
A. Chlorpromazine	B. Thiothixene	C. Olanzapine	D. Ziprasidone
2. **Cariprazine** acts at which receptor of the following?			
A. D1	B. D2	C. D3	D. D4
3. Which of the following is a side effect of **Clozapine**?			
A. Agranulocytosis	B. Hypotension	C. Impotence	D. Weight gain
4. Blocking of which receptors is responsible for weight gain?			
A.Dopaminergic	B. Serotonergic	C. Alpha receptors	D. Beta receptors
5. Blocking of which receptor is responsible for sedation?			
A.M1	B. 5HT2a	C. D3	D. H1
6. Which of the following causes **Obstructive jaundice**?			
A. Quetiapine	B. Chlorpromazine	C. Ketoconazole	D. Thioridazine
7. Which one of these drugs is contraindicated in patients with **prolonged QT** interval?			
A. Risperidone	B. Cariprazine	C. Clozapine	D. Olanzapine

1:C ,2:C ,3:A ,4:B ,5:D ,6:B ,7:A

SAQ

01

Mention 3 examples of typical Antipsychotic drugs and their MOA.

Chlorpromazine, Thioridazine, Haloperidol.

Acts by blocking dopaminergic receptors.serotonin, adrenergic, cholinergic, and histaminergic receptors.

02

What is Neuroleptic malignant syndrome?

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

Team Leaders

Muhannad Al-otabi

Reema Almotairi

Sarah Alajaji

Maryam Alghannam

Team members

Abdulaziz Alamri

Faisal Alateeq

Nazmi M Alqutub

Sultan Almishrafi

Mohammed Maashi

Mohammed Alasmary

Nazmi A Alqutub

Ziad Alhabardi

Mohammed Alrobeia

Mohammed Alhudaithi

Sami Mandoorah

Omar Alamri

Mohammed Alqutub

Reena Alsadoni

Almas Almutairi

Fatimah Alghamdi

Lama Alotaibi

Salma Alsaadoun

Jouri Almaymoni

Faisal alzuhairy

Salma Alkhlassi

Huda bin jadaan

Manar Aljanubi

Wasan Alanazi

Jana Almutlaqah

Farah Abukhalaf

Norah Almalik

Rawan Alqahtani

Aroub Almahmoud

Remaz Almahmoud

Special thanks to norah almania for the amazing logo