MEDICINE
KING SAUD UNIVERSITY

436 team
pharmacology

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:

- extra information and further explanation
- important
- doctors notes
- Drugs names
- Mnemonics

تمت المراجعة
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Check out the mnemonics file :
https://docs.google.com/presentation/d/1Z0Vf9oEOJSXo4JIA0mTCk5jB-OU9LP5TFCwz8iBgNac/edit?usp=sharing

Kindly check the editing file before studying this document
https://docs.google.com/presentation/d/1_-g1vol4eBWPet5xVCkuTGFvvnhFF3PJmU0tWtEEw_o/edit?usp=sharing

Introduction

Psychoses :

- Schizophrenia affect thoughts
- Affective Psychoses affects mood
  - Mania.
  - Depression
  - Manic-depressive illness (bipolar affective disorder).

Schizophrenia

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

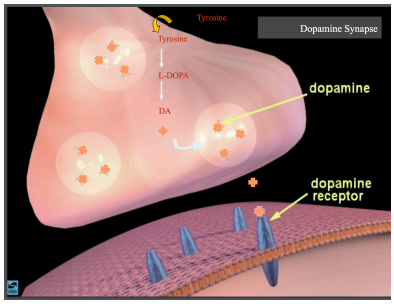
Positive Symptoms	Negative Symptoms (FAMILY MEMBERS notice these changes not the patient)
1. Hallucinations. 2. Delusions. 3. Paranoia.	1. Social withdrawal. 2. Anhedonia (absence of pleasure). 3. Emotional blunting.

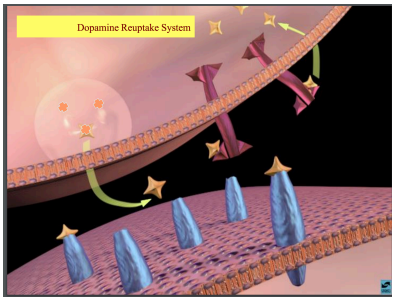
Dopamine System

Dopaminergic pathways in the brain :

Schizophrenia drugs affect all the pathways

1- **Mesolimbic-mesocortical** pathway schizophrenia drugs have therapeutic effect on these pathways	**behavior**
2- Nigrostriatal pathway	co-ordination of voluntary **movements**
3- Tuberoinfundibular pathway	**endocrine effects**
4- Medullary-periventricular pathway	(**metabolic effects**)





Most of schizophrenia drugs side effects comes from blocking D2 receptors in pathways other than Mesolimbic-mesocortical . If we avoid blocking D2 so, we avoid these side effects

DOPAMINE RECEPTORS :

There are at least five subtypes of receptors:

D 1, D 2, D 3, D 4, D 5

D2 is the classical dopamine receptor

Antipsychotic drugs

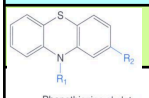
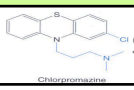
What are they ?

are group of drugs used in the treatment of schizophrenia.
-Old name (neuroleptic drugs)

Classification:

Drugs used in schizophrenia are classified according to **chemical structures** Into	
Typical	**Atypical** **Better!**
discovered first, **non selective**, **many** side effects, **rarely** used nowadays.	more selective, less side effects, **1st** line treatment for schizophrenia.

Classification of antipsychotic drugs

 Phenothiazine skeleton **Typical** Antipsychotic Drugs→ **affect D2 mainly Except Cariprazine on D3 → treat the +ve symptoms.**	
Phenothiazine derivatives Its chemical structure similarto TCAs →similar ADRs	 Chlorpromazine Such as: **Chlorpromazine**(Protype very old),**Thioridazine**
Butyrophenones	Such as: **Haloperidol**
Thioxanthene	Such as: **Thiothixene**
Atypical Antipsychotic Drugs better than typical → **Affect both DA & 5-HT receptors →treat +ve & -ve symptmos.**	
Dibenzodiazepines	Such as: **Clozapine**
Benzisoxazoles	Such as: **Risperidone**
Thienobenzodiazepines	Such as: **Olanzapine**
Dibenzothiazepines	Such as: **Quetiapine**
Benzisothiazoles	Such as: **Ziprasidone**
piperazine/piperidine derivatives	Such as: **Cariprazine** **(approved in 2015 by the FDA)**

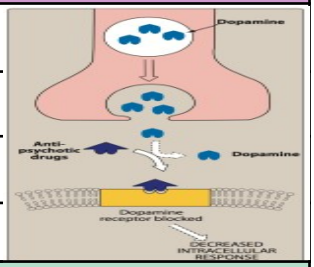
The pharmacological action of antipsychotic drugs result from

Blocking **dopamine** receptors at different areas in the brain.

Blocking **muscarinic** receptors

Blocking **α-adrenergic** receptors

Blocking **H1 receptors**



Adverse effects on CNS	Advantages of Atypical drugs
They are due to blocking dopamine receptors at areas other than mesolimbic area **(extrapyramidal effects).**	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

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

Antipsychotic effect	**Its effect:**	**(it's the main use).** It takes from 10 days to 3 weeks to start its action - Produce emotional quieting and psychomotor slowing. - Decreasing hallucinations, delusions and agitation.
	Mechanism:	blockage of **dopamine** receptors in the mesolimbic system. →treat +ve symptoms. *Atypical drugs exert their antipsychotic action through blocking serotonergic (5HT2) and dopaminergic receptors→. treat –ve symptoms also.
Extrapyramidal symptoms	**Its effect:**	EXTRAPYRAMDAL = PARKINSOMISM LIKE EFFECT. - Abnormal involuntary movements such as tremors, parkinsonism, and tardive dyskinesia.
	Mechanism:	blockage of **dopamine** receptors in the **nigrostriatum**.
Endocrine effects	**Its effect:**	- Galactorrhea - Amenorrhea cause false +ve pregnancy test (female) - Gynecomastia & impotence. → For male
	Mechanism:	prevent **dopamine** from inhibiting prolactin release from pituitary gland and that will lead to hyperprolactinemia.

Metabolic effect:	**Its effect:**	changes in eating behavior and weight gain.
	Mechanism:	blockage of **dopamine** receptors in the medullary-periventricular pathway.
Antiemetic effect:	**Its effect:**	Effective against drug and disease- induced vomiting. (not-motion sickness)
	Mechanism:	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.

Pharmacological actions Cont.

		ANS	Other
Anticholinergic effects	Its effect:	-Blurred vision -Dry mouth -Urinary retention -Constipation	*very important **Temperature regulation:** Beneficial effect May cause lowering of body temp. **Mechanism:** heat loss as a result of vasodilation due to **alpha1-blocking** or central effect.
	Mechanism:	blockage of **muscarinic** receptors.	*very important **ECG changes:** prolongation of QT interval, abnormal configuration ST segment and T wave. **c.I : in cardiac patients**
Antiadrenergic effects	Its effect:	- Postural hypotension - Impotence - failure of ejaculation.	**Antihistaminic effect :** *very important sedation due to **H1 receptor blockage**.
	Mechanism:	blockage of **alpha1-adrenergic** receptors. NOTE: Non of the atypical group causes antiadrenergic effect.	*very important **Quinidine-like action:** Anti-arrhythmic drug Increasing action potential duration as well as prolonged QT interval. It causes arrhythmia

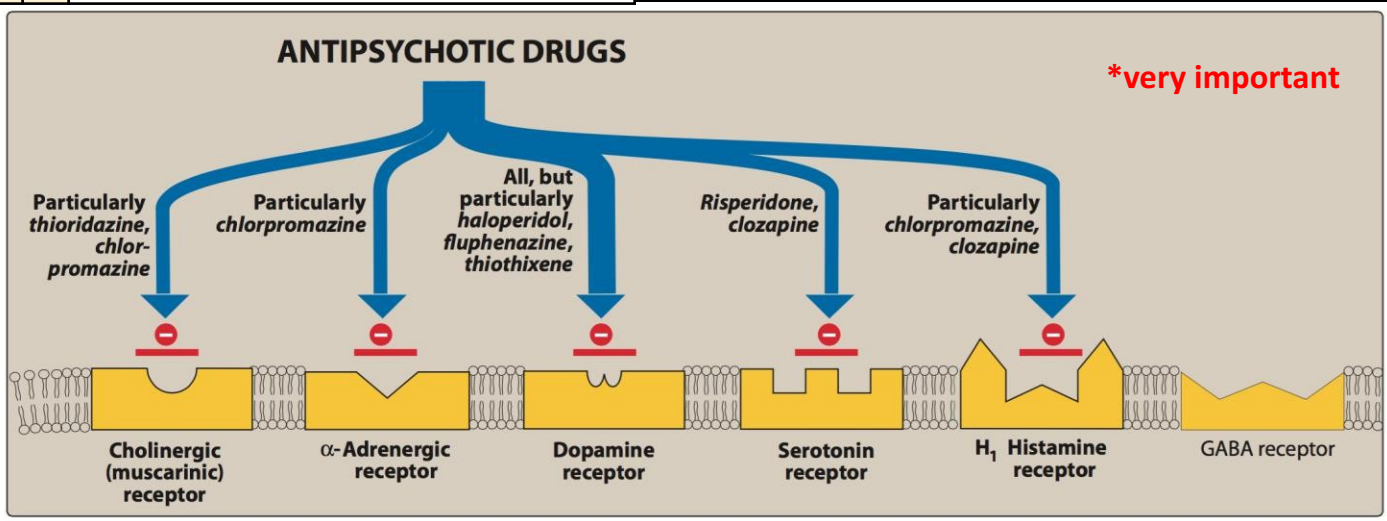


Figure 13.4
Antipsychotic drugs block at dopaminergic and serotonergic receptors as well as at adrenergic, cholinergic, and histamine-binding receptors. GABA = γ-aminobutyric acid.

Adverse effects Unwanted pharmacological effects

CNS

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

2- Extrapyramidal symptoms: →Some occurring early (Parkinson's syndrome) ,other late occurring

A) Tardive Dyskinesia (IRREVERSIBLE MANIFSTATION if we don't stop the drug) Due to prolong use	B) Neuroleptic Malignant Syndrome Has a genetic element
• (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.).

ANS

1- Anticholinergic Effects :	2- Antiadrenergic Effects :
• Blurred vision. • Dry mouth. • Urinary retention. • Constipation→ Such as with: **Chlorpromazine** (typical), **Clozapine** (atypical)	• Postural hypotension. • Impotence • Failure of ejaculation. **Chlopromazine** (typical) يجمع كل الاعراض الجانبية المعروفة **Thioridazine** (typical)

Endocrine Effects:

- Gynecomastia
- Gynecomastia
- Amenorrhoea

Miscellaneous Effects:

- Obstrucive jaundice
- Granular deposits in cornea
- Retinal deposits (Only thioridazine)
- Weight gain Mostly Atypical

Clozapine

Agranulocytosis(life threating) *very important

- 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
➢ **Schizophrenia** (**primary indication**) ➢ Acute mania ➢ Manic-depressive illness (bipolar affective disorder) **during the manic phase** Atypical 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.	➢ Nausea and vomiting (**prochlorperazine and benzquinamide**) Only used as antiemetics ➢ Pruritis (Itching because of anti-histamine effect) ➢ Preoperative sedation **(rare use)**

Pharmacokinetics:

- Incompletely absorbed.
- Highly **lipid soluble**.(So it can cross BBB)
- Highly bound to plasma proteins.
- Undergo extensive **first-pass hepatic metabolism.**
- Excretion by the kidney

Atypical Antipsychotics

What are they ?

- 2nd Generation antipsychotics
- Now considered as **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.

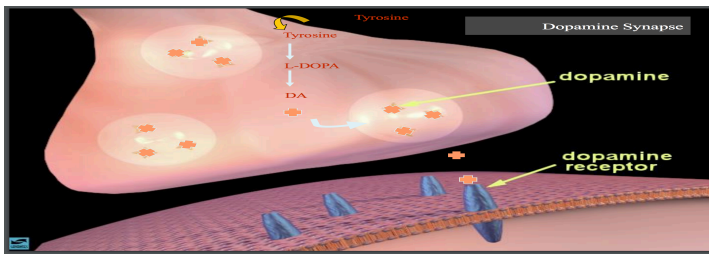
Atypical Antipsychotics

*very important

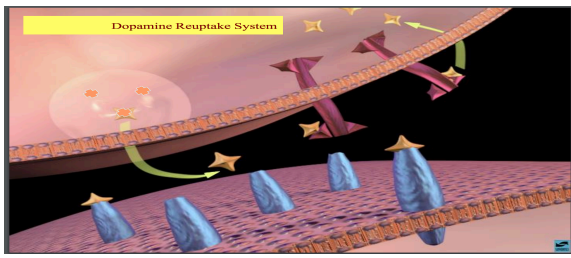
Drug	Risperidone	Remember it's Atypical Ziprasidone	Clozapine	Olanzapine	Quetiapine	Cariprazine
Mech. of action	Blocks D2 & 5HT2 receptors.	Blocks D2 & 5HT2 receptors	Blocks both D4 & 5HT2 receptors.	Blocks D1 - D4 & 5HT2 receptors.	Blocks D1 -D2 & 5HT2 receptors	approved in 2015 by the FDA - has higher affinity at D3 receptor
Indications		Drug interactions: - Should not be used with any drug that prolongs the QT interval. - Activity decreased by carbamazepine (inducer of CYP3A4) - Activity increased by ketoconazole (antifungal) (inhibitor of CYP3A4)				has a positive impact on the cognitive symptoms of schizophrenia
ADRs	- Postural hypotension - QT prolongation - Weight gain	- Drowsiness, Akathisia (cant keep still) ,Headache ,Dizziness, Weight gain.	Agranulocytosis - Seizures - Myocarditis - Excessive salivation (during sleep)	- Weight gain - -Sedation Flatulence, increased salivation & thirst. - Postural hypotension.	- Sedation Hypotension Sluggishness - Dry mouth - Increased appetite (weight gain) - Abdominal pain - Constipation	
Contra-indications	Patients with long QT interval.	It increases mortality in elderly patients with dementia-related psychosis.	it contraindicated in patient with epilepsy			

Summary

- ➢ 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**



The synapse and synaptic neurotransmission
Describe the synapse and the process of chemical neurotransmission. Indicate how vesicles containing a neurotransmitter, such as dopamine (the stars), move toward the presynaptic membrane as an electrical impulse arrives at the terminal. Describe the process of dopamine release (show how the vesicles fuse with the presynaptic membrane). Once inside the synaptic cleft, the dopamine can bind to specific proteins called dopamine receptors (in blue) on the membrane of a neighboring neuron. Introduce the idea that occupation of receptors by neurotransmitters causes various actions in the cell; activation or inhibition of enzymes, entry or exit of certain ions. State that you will describe how this happens in a few moments



Dopamine binding to receptors and uptake pumps in the nucleus accumbens
Explain that cocaine concentrates in areas of the brain that are rich in dopamine synapses. Review dopamine transmission in the nucleus accumbens. Point to dopamine in the synapse and to dopamine bound to dopamine receptors and to uptake pumps on the terminal.

إِنَّ فِي ذَٰلِكَ لَآيَاتٍ لِّقَوْمٍ يَتَفَكَّرُونَ ﴿٣﴾

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References :

1- 436 doctors slides
2-435 team work

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