Pharmacology Team 431

(CNS BLOCK)

[Drug Used in Schizophrenia]

Done by :

Mohammed Al-Shammari

Abrar Al-Lafi

Drugs Used in Schizophrenia

Schizophrenia: happened due to increase in dopamine , serotonin levels

Introduction:

- **Psychosis has two divisions:**

1- Affective Psychosis:

Affective :related to the mood.

a- Mania

b- Depression

c- Manic-depressive illness (bipolar affective disorder)

2- Schizophrenia: Basic thinking disturbances.

- **Symptoms of Schizophrenia:**

A- Positive Symptoms:

- **Hallucinations.**
- **Delusion. "Visual or auditory"**
- **Paranoia: Suspicious to people "always thinking that everyone trying to do harm for him/her."**

A- Positive Symptoms:

- more common
- Can be treated by both typical and atypical groups.

B- Negative symptoms:

- Can be treated only by the atypical group.

B- Negative Symptoms:

- **Social withdrawal,**
- **Anhedonia (absence of pleasure)**
- **Emotional blunting: does not react with happiness or sadness "e.g pt. may laugh when his mother died"**

Dopamine System:

- **Dopaminergic pathways in the brain:**

1- Mesolimbic - mesocortical pathway:

for behavior

2- Nigrostriatal pathway:

for co-ordination of voluntary movements.

3- Tuberoinfundibular pathway:

endocrine effects

4- Medullary - periventricular pathway:

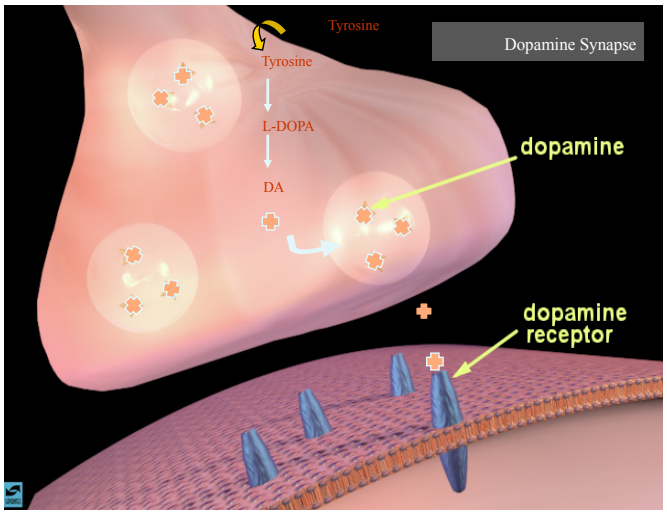
metabolic effects

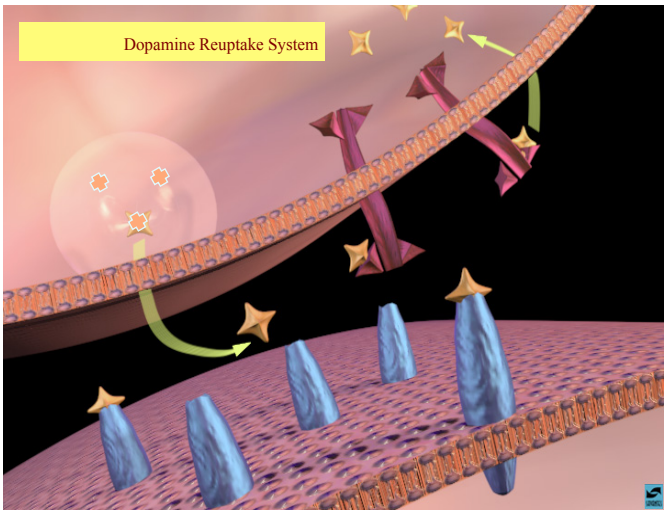
Notice that: Blocking of dopamine in each system produce different effects as we will see.

- **Dopamine Receptors:**

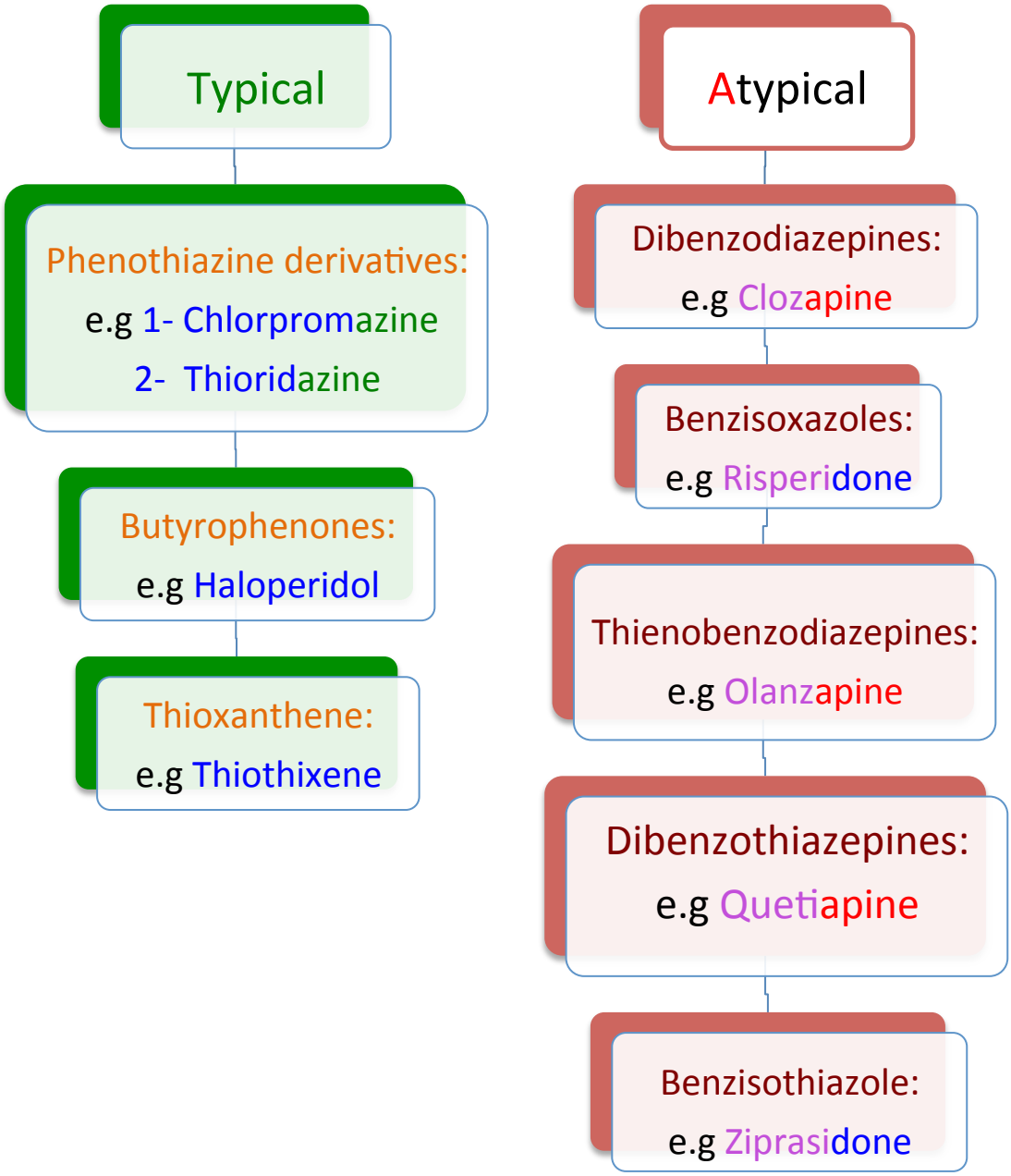
There are at least five subtypes of receptors:

D1, D2, D3, D4, D5





Antipsychotic drugs



Typical: old generation

Atypical: 2nd generation , less side effect , more effective.

***more details about them , found below**

Pharmacological Actions

what's the effects of these drugs in Normal people?
Sedation , Dysphoria that's why nobody will be addicted to it!

CNS:

1- **Antipsychotic effect**:

- Produce emotional quieting and psychomotor slowing.
- Decrease hallucinations, delusions and agitation.

❖ Mechanism:

Blockade of dopamine receptors in the mesolimbic system.

2- **Extrapyramidal Symptoms**:

- Abnormal involuntary movements such as tremors, parkinsonism & tardive dyskinesia*

*explained later

❖ Mechanism:

Blockade of dopamine receptors in the nigrostriatum.

3- **Endocrine effects**:

Galactorrhea: secretion of milk from the breast without pregnancy or nursing.
, amenorrhea: stoppage of the menstrual period.
, gynecomastia: Enlargement of the breast in the male.
& impotence.

❖ Mechanism:

Prevent dopamine inhibition of prolactin release from pituitry→ Hyperprolactinemia.

pituitary gland secrete prolactin, the dopamine inhibit the pituitary from secreting the prolactin, so if the dopamine is inhibited => the prolactin will be released in high amount=> Hyperprolactinemia.

4- Metabolic effects

Changes in eating behavior and weight gain.

❖ Mechanism:

Blockade of dopamine receptors in the medullary – periventricular pathway.

5- Anti-emetic effect:

Effective against drug & disease- induced vomiting

(not- motion sickness).

❖ Mechanism: Blockade of dopamine receptors in the Chemoreceptor Trigger Zone (CTZ) of the medulla.

ANS:

1- Anticholinergic Effects:

- Blurred vision
- Dry mouth
- Urinary retention
- Constipation

❖ Mechanism: Blockade of muscarinic receptors.

2- Antiadrenergic Effects:

- Postural hypotension
- Impotence
- Failure of ejaculation

❖ Mechanism: Blockade of α- adrenergic receptors.

Other Actions:

1- **Temperature regulation :**

May cause lowering of body temperature

Mechanism: "actually not well understood, but there're some theories"

Heat loss as a result of vasodilation (α- blocking) Or due to central effect.

Some people say , How vasodilation cause hypothermia "low body temperature"? , so I just copied this from wiki:

Vasodilation and sweating are the primary modes by which humans attempt to lose excess body heat. The brain creates much heat through the countless reactions which occur. Even the process of thought creates heat. The head has a complex system of blood vessels, which keeps the brain from overheating by bringing blood to the thin skin on the head, allowing heat to escape.

2- **ECG changes :**

- **Prolongation of QT interval**
- **Abnormal configuration of ST- segment & T wave**

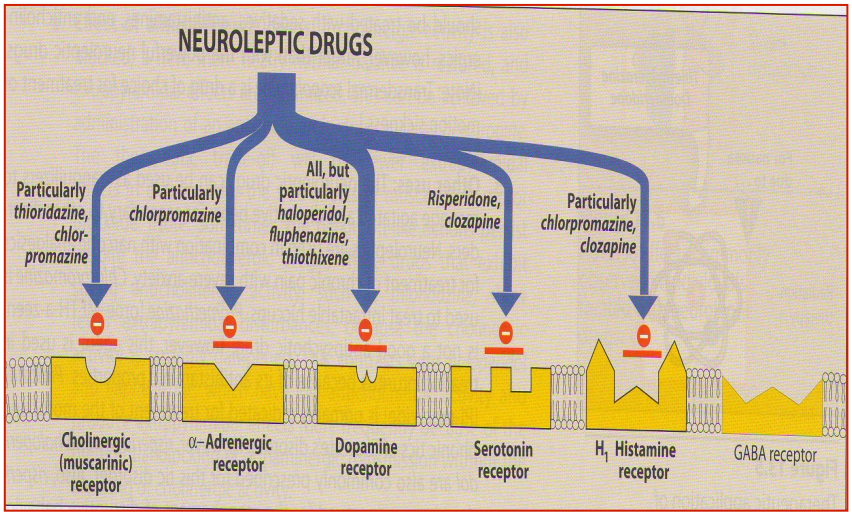
3- **Antihistaminic effect :**

- **Sedation**

Mechanism: due to H1 receptor blockade

4- **Quinidine -like actions.**

This diagram shows how theanti-psychotics "Especially the Typical" are totally **non-selective** and act in too many receptors



Therapeutic Uses

Psychotic:

- **Schizophrenia (primary indication).**
- **Acute mania.**
- **Manic-depressive illness (bipolar affective disorder) during the manic phase.**

Non-Psychotic:

1- Nausea and vomiting

- prochlorperazine and benzquinamide

are only used as antiemetics

because their anti-psychotic action is low.

2- Pruritis

because of the anti-histamine action , but there're better drugs for Pruritis.

3- Preoperative sedation (rare use)

"But Benzodiazepines are better used in preoperative sedation"

Preoperative sedation: sedation of the patient before an operation e.g surgery

Adverse Effects

On CNS:

1- Sedation, drowsiness, fatigue: "because of histamine blockade "H1"

(haloperidol , Risperidone)

2- Extrapyramidal symptom:

Some occurring early in treatment as :

Parkinson's syndrome

Other Extrapyramidal Symptoms are late - occurring :

1- Tardive Dyskinesia. "irreversible side effect !"

from Latin tardus (slow or late coming)

it is a disorder of involuntary movements (choreoathetoid movements of lips, tongue, face, jaws, and of limbs and sometimes trunk).

"You job as doctor prevent this side effect, by discontinue and change the drug or lower the dose, when u see the early occurring symptoms"

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.

On ANS:

1- Anticholinergic Effects :

- Blurred vision
- Dry mouth
- Urinary retention
- Constipation

(Clozapine, Chlorpromazine)

2- Antiadrenergic Effects :

- Postural hypotension
- Impotence
- Failure of ejaculation

(Chlopromazine , Thioridazine)

3- Endocrine Effects :

(Hyperprolactinemia)

- Gynecomastia
- Galactorrhoea
- Amenorrhoea

Miscellaneous Effects:

- Obstrucive jaundice
- Granular deposits in cornea
- Retinal deposits (thioridazine)
- Weight gain
- Agranulocytosis "drop in WBCs because the bone marrow no more produce WBCs" (Clozapine) about 1-2% usually happen after 6-18 weeks "Weekly WBC checking is mandatory"
- Seizures (Clozapine)

Pharmacokinetics

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

More details about Atypical Anti-Psychotics

Features:

- **2nd Generation antipsychotics**
- **Are now considered to be 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.**

"While the typical block dopaminergic but not serotonergic ,and they act mainly on +ve symptoms"

Clinical Uses of Atypical Anti-psychotics:

- **Refractory cases of schizophrenia.**

"But doctors use it as 1st line, to avoid complications and side effects of the typical"

- **To reduce the risk of recurrent suicidal behavior in patients with schizophrenia.**

Examples of Atypical Anti-Psychotics:

- ## Clozapine:

Mechanism:

Blocks both D4 & 5HT2 receptors.

Main adverse effects:

- Agranulocytosis
- Seizures
- Myocarditis
- Excessive salivation (during sleep) "Strange side effect, although they have Anti-Cholinergic "cause mouth dryness" and they cause Salivation during sleep!"

- ## Risperidone:

Mechanism:

Blocks D2 & 5HT2 receptors.

Main adverse effects:

- Postural hypotension
- QT prolongation
- Weight gain

Contraindicated in patients with long QT interval

- ## Olanzapine:

Mechanism:

Blocks D1- D4 & 5HT2 receptors

Main adverse effects:

- Weight gain
- Sedation
- Flatulence , increased salivation & thirst
- Postural hypotension

- ## Quetiapine:

Mechanism:

Blocks D1-D2 & 5HT2 receptors

Main adverse effects:

- Sedation
- Hypotension
- Sluggishness "effect less than drowsiness"
- Dry mouth
- Increased appetite (weight gain)
- Abdominal pain
- Constipation

- Ziprasidone :

Mechanism:

Blocks D2 & 5HT2 receptors.

Main adverse effects:

- Drowsiness
- Akathisia "restlessness result in aimless movement"
- Headache
- Dizziness
- Weight gain

Drug interactions: "important"

- should not be used with any drug that prolongs the QT interval.
- Activity decreased by carbamazepine "antiepileptic drug" (inducer of CYP3A4)
- Activity increased by ketoconazole (inhibitor of CYP3A4)

 # WARNING

Ziprasidone INCREASE MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS.

Summary

- Drugs used in schizophrenia are classified according to chemical structures.
- The advantages of Atypical drugs include :

1. They block both dopaminergic & serotonergic drugs.
2. They are effective in refractory cases of schizophrenia.
3. They produce few extrapyramidal effects.

- The pharmacological actions of antipsychotic drugs result from :

1. Blocking dopamine receptors at different areas in the brain.
2. Blocking muscarinic receptors.
3. Blocking α-adrenergic receptors.
4. 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:

1. Clozapine
2. Risperidone
3. Olanzapine
4. Quetiapine
5. Ziprasidone

Questions

Which of the following dopaminergic systems is most closely related to behavior?

a) The hypothalamic-pituitary system
b) The extrapyramidal system
c) The mesolimbic and mesofrontal systems
d) The chemoreceptor trigger zone of the medulla

Which of the following antipsychotic drugs has high affinity for D4 and 5-HT2 receptors?

a) Clozapine
b) Fluphenazine
c) Thioridazine
d) Haloperidole

Which of the following antipsychotic drugs has the high risk of potentially fatal agranulocytosis and risk of seizures at high doses?

a) Haloperidol
b) Risperidone
c) Clozapine
d) Chlorpromazine

Answers: C , A , C

Thanks and Good Luck