

# Drugs used in schizophrenia

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# Objectives

At the end of the lecture , students should be able to :

- 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.

# Objectives ( con.)

- ▶ 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.

**Drugs used in the treatment of schizophrenia are called :**

**Antipsychotic drugs**

old name ( neuroleptic drugs)

# PSYCHOSES

## 1- Affective Psychoses:

a- Mania

b- Depression

c- Manic-depressive illness  
( bipolar affective disorder )

## 2- Schizophrenia

# Schizophrenia

## **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)

# Schizophrenia

## Positive Symptoms

- ▶ **Hallucinations**
- ▶ **Delusions**
- ▶ **Paranoia**



# Schizophrenia

## Negative Symptoms

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

# Dopamine System

## Dopaminergic pathways in the brain : ▶

- 1- Mesolimbic - mesocortical pathway ▶  
(behavior)
- 2- Nigrostriatal pathway ▶  
(co-ordination of voluntary movements)
- 3- Tuberoinfundibular pathway ▶  
(endocrine effects)
- 4- Medullary - periventricular pathway ▶  
(metabolic effects)

Dopamine Synapse

Tyrosine



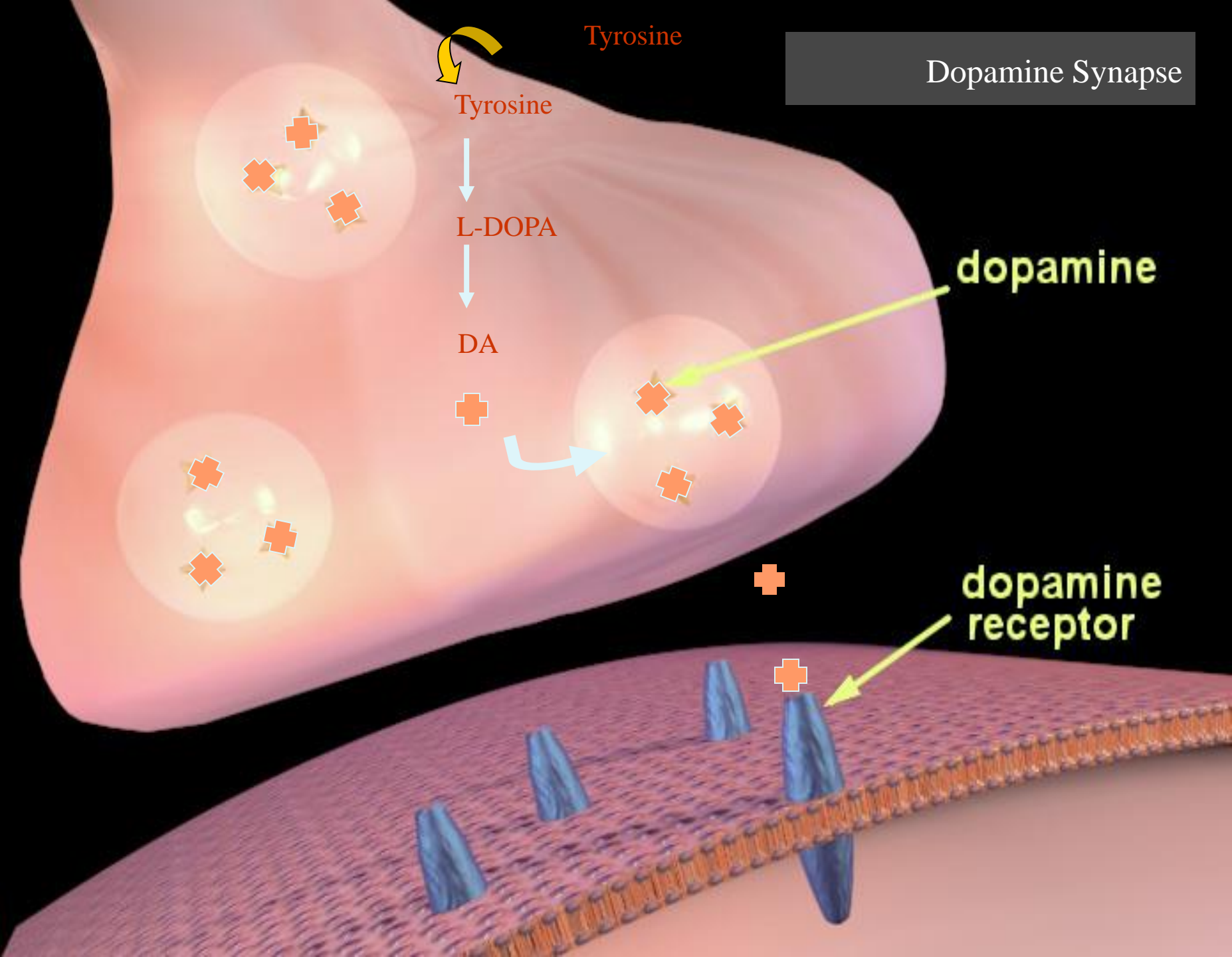
Tyrosine

L-DOPA

DA

dopamine

dopamine receptor



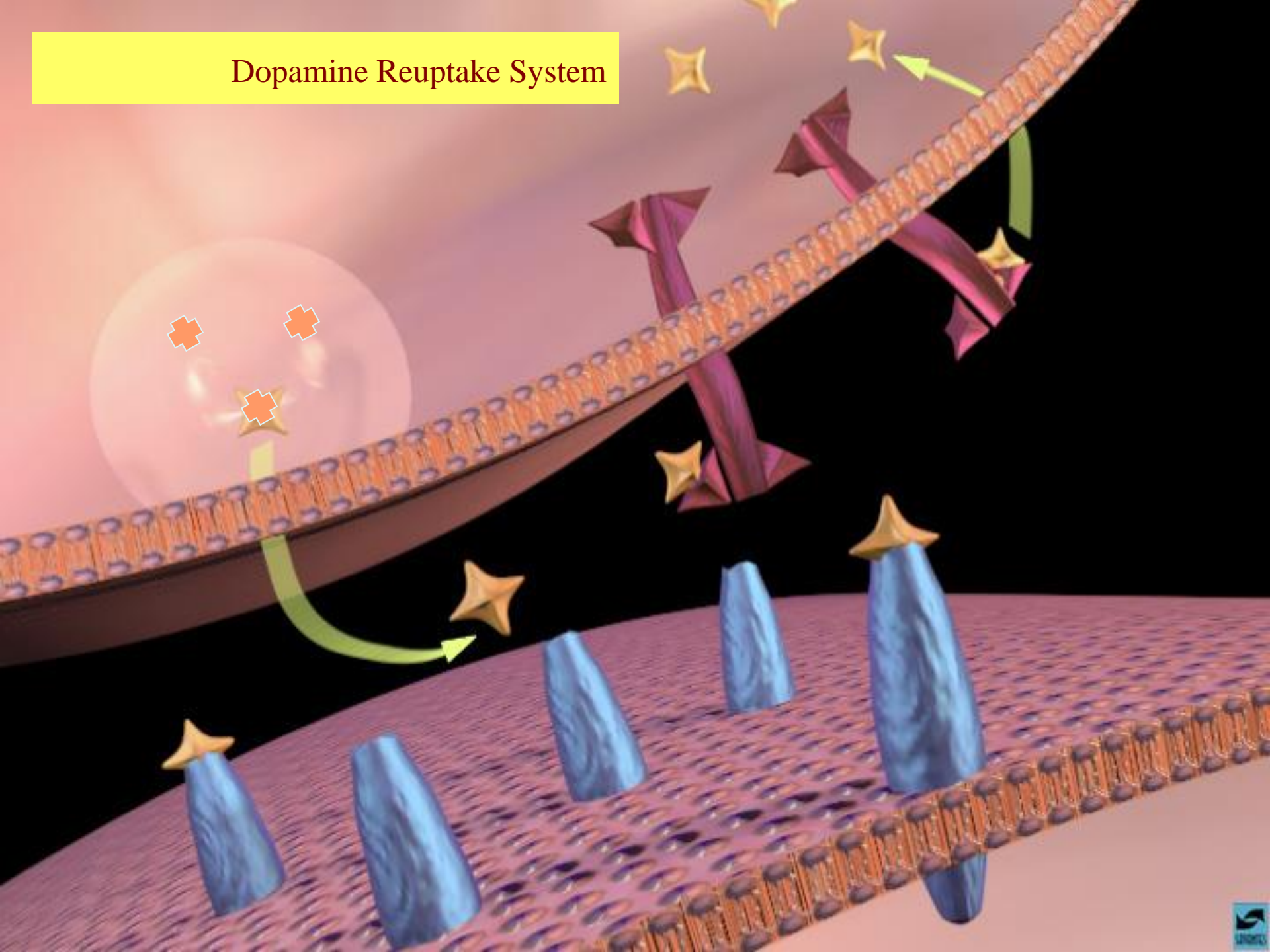
# Dopamine System

## DOPAMINE RECEPTORS

There are at least five subtypes of receptors:

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

# Dopamine Reuptake System



# Antipsychotic drugs

## Classification :

According to chemical structure into :

## Typical Antipsychotic Drugs :

### 1-Phenothiazine derivatives

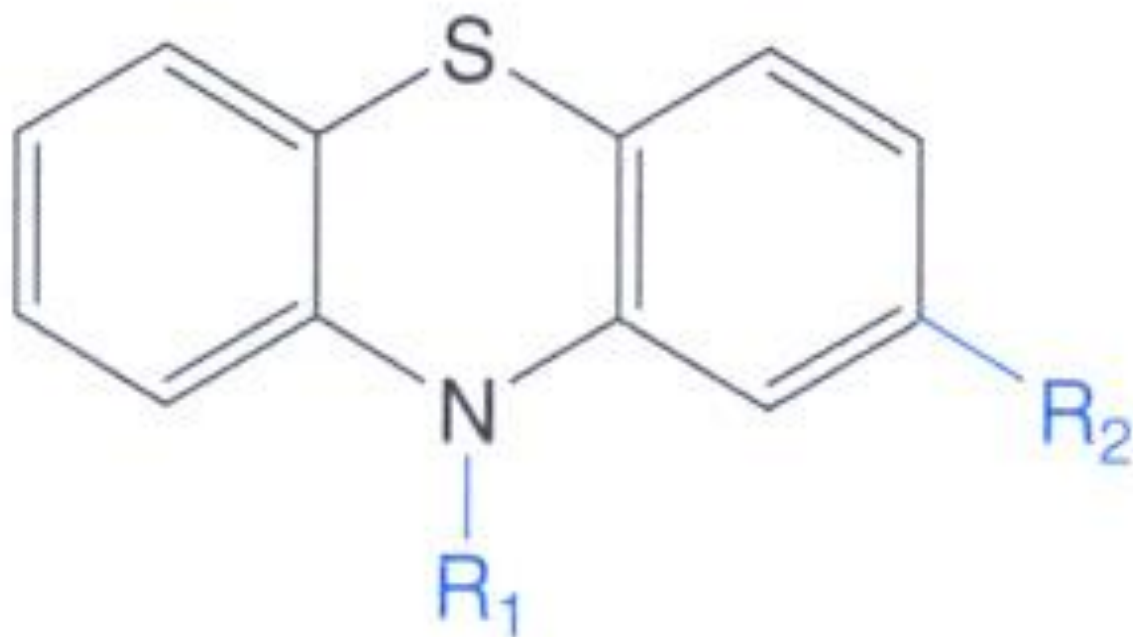
- Chlorpromazine
- Thioridazine

### 2- Butyrophenones

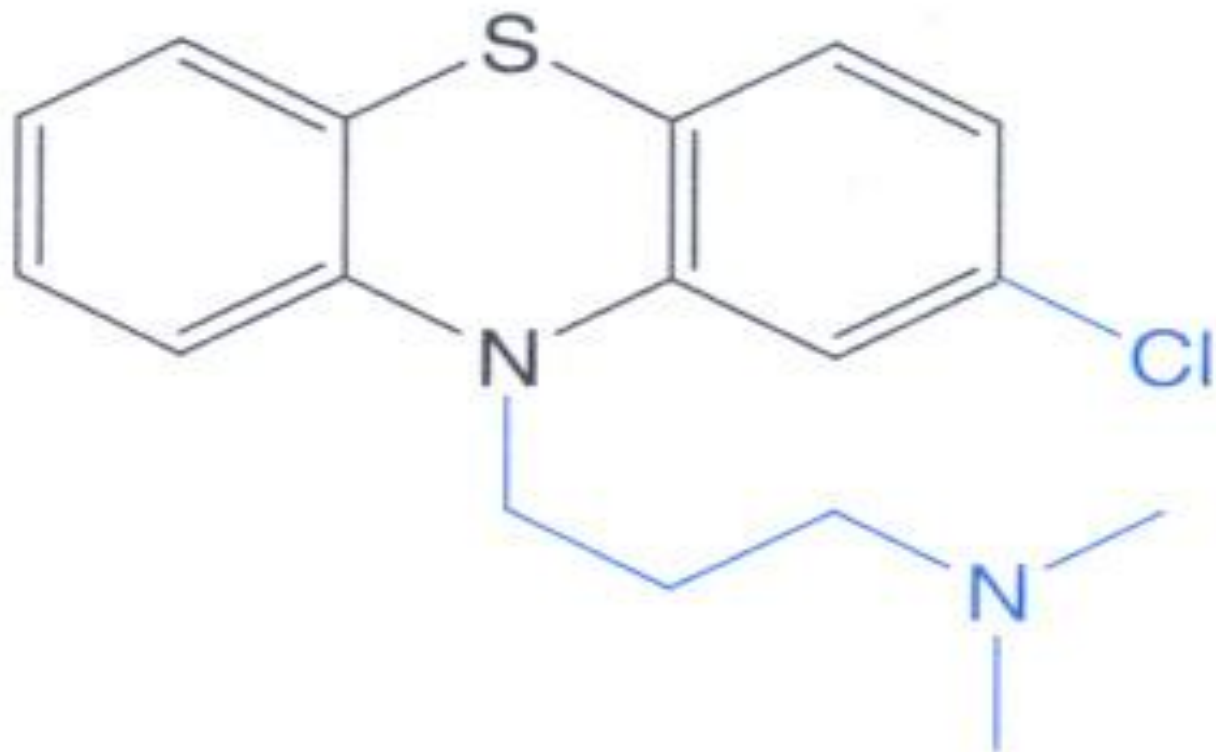
- Haloperidol

### 3- Thioxanthene

- Thiothixene



Phenothiazine skeleton



Chlorpromazine



# Antipsychotic drugs

## Classification (cont..)

### Atypical Antipsychotic Drugs :

4- Dibenzodiazepines

▶ Clozapine

5- Benzisoxazoles

▶ Risperidone

6- Thienobenzodiazepines

▶ Olanzapine

7- Dibenzothiazepines

▶ Quetiapine

8- Benzisothiazoles

Ziprasidone

9- piperazine/piperidine derivatives

Cariprazine

# Pharmacological Actions

## ▶ C.N.S :

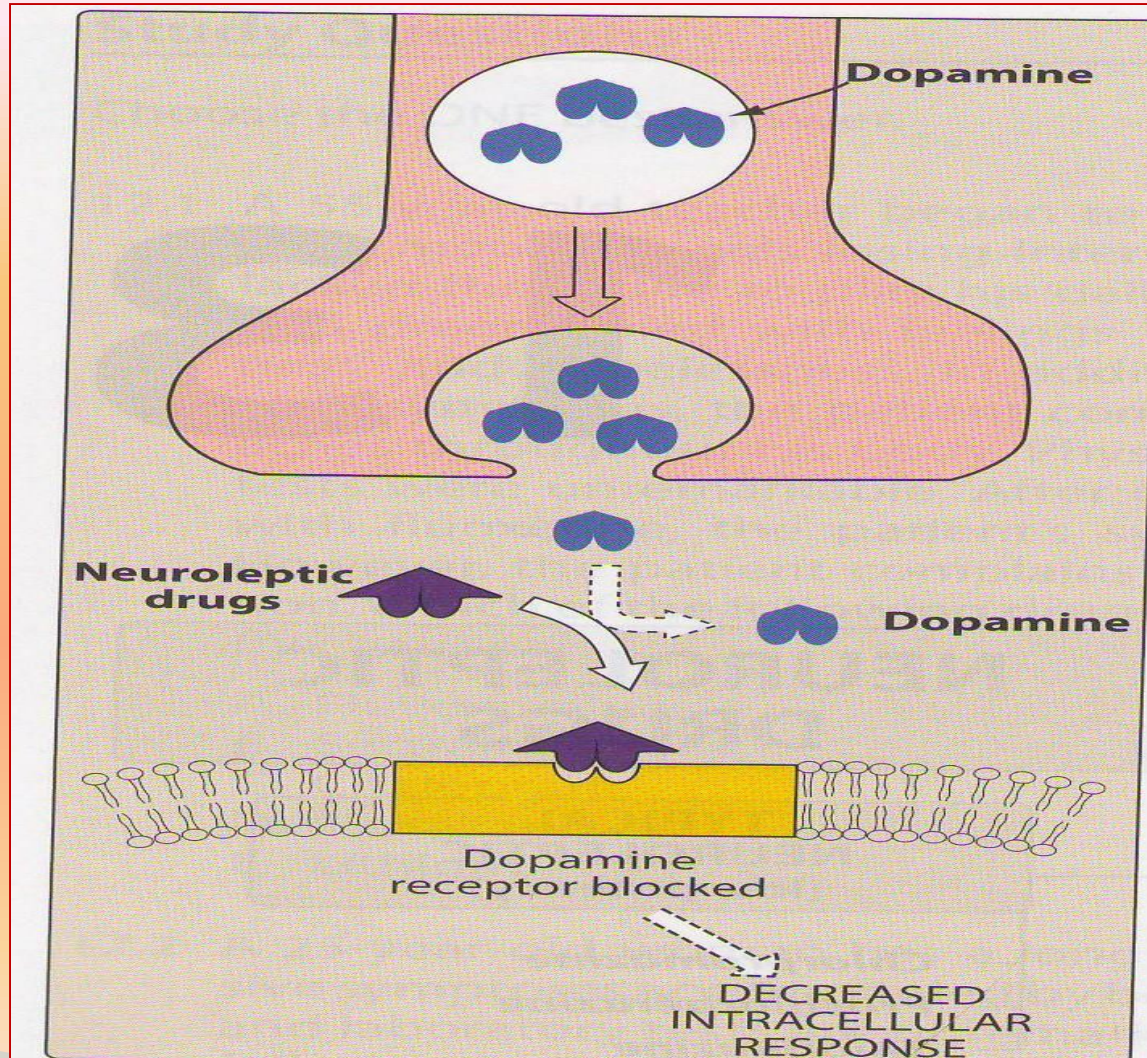
### 1 – Antipsychotic effect :

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

### Mechanism:

- ❖ Blockade of dopamine receptors in the mesolimbic system.

# Mechanism of Antipsychotic Action



- ▶ **Atypical drugs exert their antipsychotic action through blocking serotonergic ( 5HT<sub>2</sub>) & dopaminergic receptors.**

# Pharmacological actions ( con.)

## 2- Extrapyramidal Symptoms :

Abnormal involuntary movements such as tremors, parkinsonism & tardive dyskinesia.

### Mechanism :

Blockade of dopamine receptors in the nigrostriatum

### **3– Endocrine effects**

**Galactorrhea, amenorrhea, gynecomastia & impotence.**

#### **Mechanism :**

**Prevent dopamine inhibition of prolactin release from pituitry → Hyperprolactinemia**

# Pharmacological Actions ( cont.)

## 4- Metabolic effects :

Changes in eating behavior and weight gain

## Mechanism :

Blockade of dopamine receptors in the medullary – periventricular pathway

# Pharmacological Actions ( cont.)

## 5– Anti–emetic effect :

Effective against drug & disease– induced vomiting ( not– motion sickness)

## Mechanism :

Blockade of dopamine receptors in the CTZ of the medulla



# Pharmacological Actions ( con.)

## A.N.S

### 1 – Anticholinergic Effects :

- Blurred vision
- Dry mouth
- Urinary retention
- Constipation

### Mechanism

Blockade of muscarinic receptors

# Pharmacological Actions ( con.)

## 2– Antiadrenergic Effects :

- Postural hypotension
- Impotence
- Failure of ejaculation

## Mechanism :

Blockade of  $\alpha$ – adrenergic receptors

# Pharmacological Actions ( con.)

## Other Actions :

1 – Temperature regulation :

May cause lowering of body temperature

**Mechanism :**

Heat loss as a result of vasodilation

(  $\alpha$ - blocking )

Or due to central effect

# Other Actions ( con.)

**2– ECG changes :**

**Prolongation of QT interval**

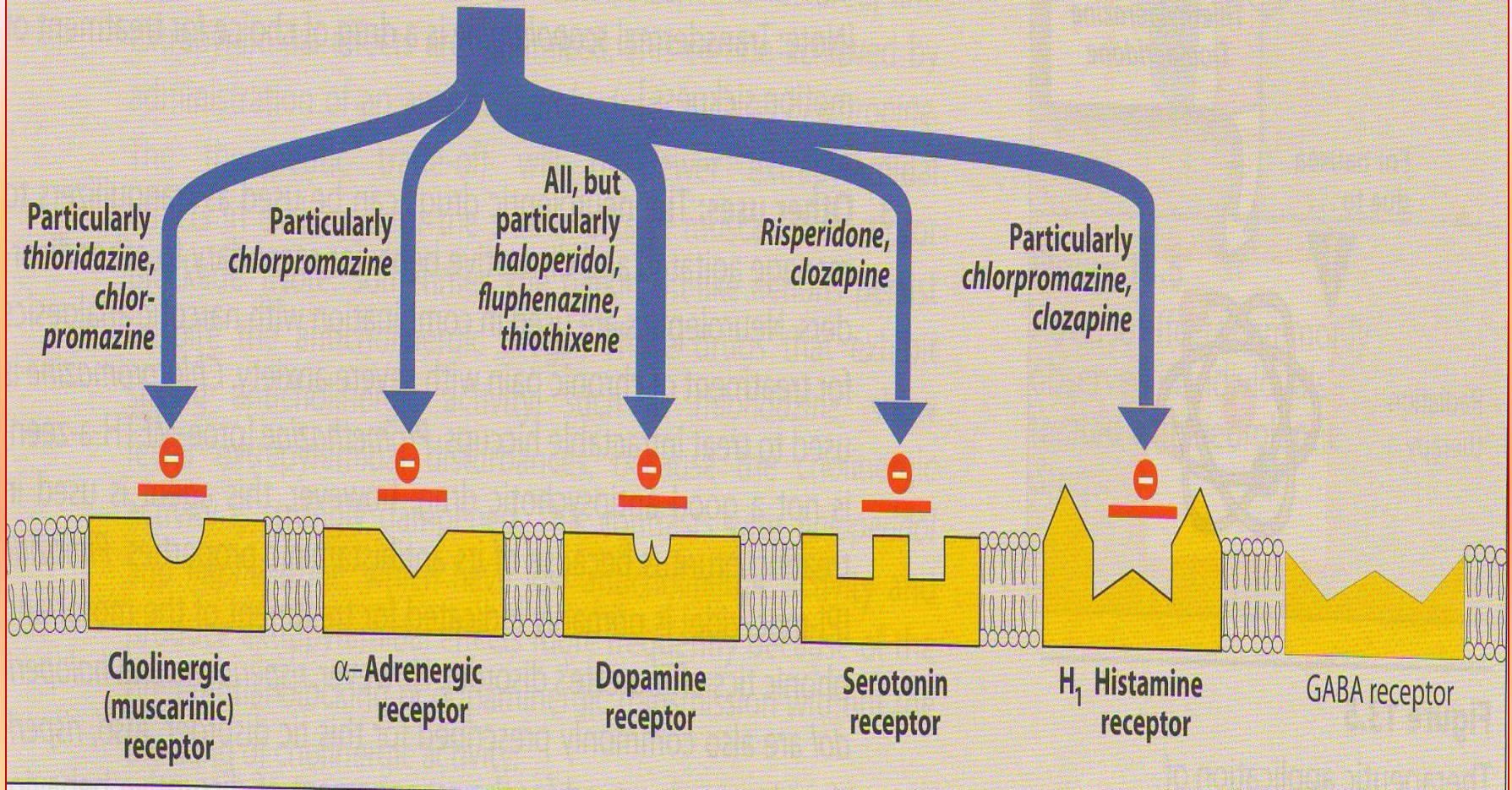
**Abnormal configuration of ST– segment & T wave.**

**3– Antihistaminic effect :**

**Sedation due to H1 receptor blockade**

**4– Quinidine -like actions**

# NEUROLEPTIC DRUGS



# Therapeutic Uses

## PSYCHIATRIC :

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

# **THERAPEUTIC USES:**

## **NON-PSYCHIATRIC:**

### **1- Nausea and vomiting**

- prochlorperazine and benzquinamide  
are only used as antiemetics**

### **2- Pruritis**

### **3- Preoperative sedation ( rare use )**

# ADVERSE EFFECTS

## C.N.S .

1 – Sedation, drowsiness, fatigue  
( haloperidol , Risperidone )

2 – Extrapyramidal symptoms :  
Some occurring early in treatment as :  
Parkinson's syndrome



# Adverse Effects ( con.)

**Other Extrapyramidal Symptoms are late – occurring :**

## **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)**

# Adverse Effects ( con.)

## 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.** ▶

# Adverse Effects ( con.)

## **A.N.S.**

### **1 – Anticholinergic Effects :**

- Blurred vision**
- Dry mouth**
- Urinary retention**
- Constipation**

**(Chlorpromazine , Clozapine )**

# Adverse Effects ( con)

## 2– Antiadrenergic Effects :

- Postural hypotension
- Impotence
- Failure of ejaculation

( Chlopromazine , Thioridazine )

# Adverse Effects ( con.)

## Endocrine Effects :

- Gynecomastia
- Galactorrhoea
- Amenorrhoea

# Adverse Effects ( con.)

- ▶ **Miscellaneous Effects :**
  - **Obstrucive jaundice**
  - **Granular deposits in cornea**
  - **Retinal deposits ( thioridazine)**
  - **Weight gain**

# Adverse Effects ( con.)

- Agranulocytosis
  - ▶ ( Clozapine ) about 1–2%
  - ▶ usually happen after 6–18 weeks
  - ▶ Weekly WBC is mandatory
  
- Seizures
  - ▶ ( Clozapine )

# PHARMACOKINETICS

- ▶ Incompletely absorbed
- ▶ Highly lipid soluble
- ▶ Highly bound to plasma proteins
- ▶ Undergo extensive first-pass hepatic metabolism.
- ▶ Excretion by the kidney



# Atypical Antipsychotics

- **2<sup>nd</sup> 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.**

# CLINICAL USES

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

# CLOZAPINE

**Blocks both D<sub>4</sub> & 5HT<sub>2</sub> receptors**

**Main adverse effects**

**Agranulocytosis**

**Seizures**

**Myocarditis**

**Excessive salivation ( during sleep )**

# RISPERIDONE

- ▶ **Blocks D<sub>2</sub> & 5HT<sub>2</sub> receptors**
- ▶ **Main adverse effects**
  - Postural hypotension
  - QT prolongation
  - Weight gain

**Contraindicated in patients with long QT interval**

# OLANZAPINE

- ▶ **Blocks D<sub>1</sub>– D<sub>4</sub> & 5HT<sub>2</sub> receptors**
- ▶ **Main adverse effects**
  - **Weight gain**
  - **Sedation**
  - **Flatulence , increased salivation & thirst**
  - **Postural hypotension**

# QUETIAPINE

- ▶ Blocks D<sub>1</sub>-D<sub>2</sub> & 5HT<sub>2</sub> receptors
- ▶ Main adverse effects
  - Sedation
  - Hypotension
  - Sluggishness
  - Dry mouth

# QUETIAPINE

- ▶ **adverse effects ( continued..)**
  - **Increased appetite ( weight gain)**
  - **Abdominal pain**
  - **Constipation**



# Ziprasidone

- Blocks D2 & 5HT2 receptors

## Main adverse effects

- Drowsiness
- Akathisia
- Headache
- Dizziness
- Weight gain

# Ziprasidone

## 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 ( inhibitor of CYP3A4 )

# Ziprasidone

## WARNING

INCREASE MORTALITY IN ELDERLY PATIENTS  
WITH DEMENTIA-RELATED PSYCHOSIS

# Cariprazine

- approved in 2015 by the FDA
- has higher affinity at D3 receptor
- has a positive impact on the cognitive symptoms of schizophrenia

# 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

# Summary (con.)

- ▶ The pharmacological actions of antipsychotic drugs result from :
  - ▶ Blocking dopamine receptors at different areas in the brain.
  - ▶ Blocking muscarinic receptors
  - ▶ Blocking  $\alpha$ -adrenergic receptors
  - ▶ Blocking H1 receptors
- ▶ Adverse effects on CNS are due to blocking dopamine receptors at areas other than mesolimbic area

# Summary ( con.)

- ▶ Blockade of H1, muscarinic &  $\alpha$ -adrenergic receptors.
- ▶ The main clinical use is in schizophrenia
- ▶ Examples of atypical drugs includes :
  - Clozapine
  - Risperidone
  - Olanzapine
  - Quetiapine
  - Ziprasidone