

Drugs used in schizophrenia

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.

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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)

Tyrosine

Dopamine Synapse

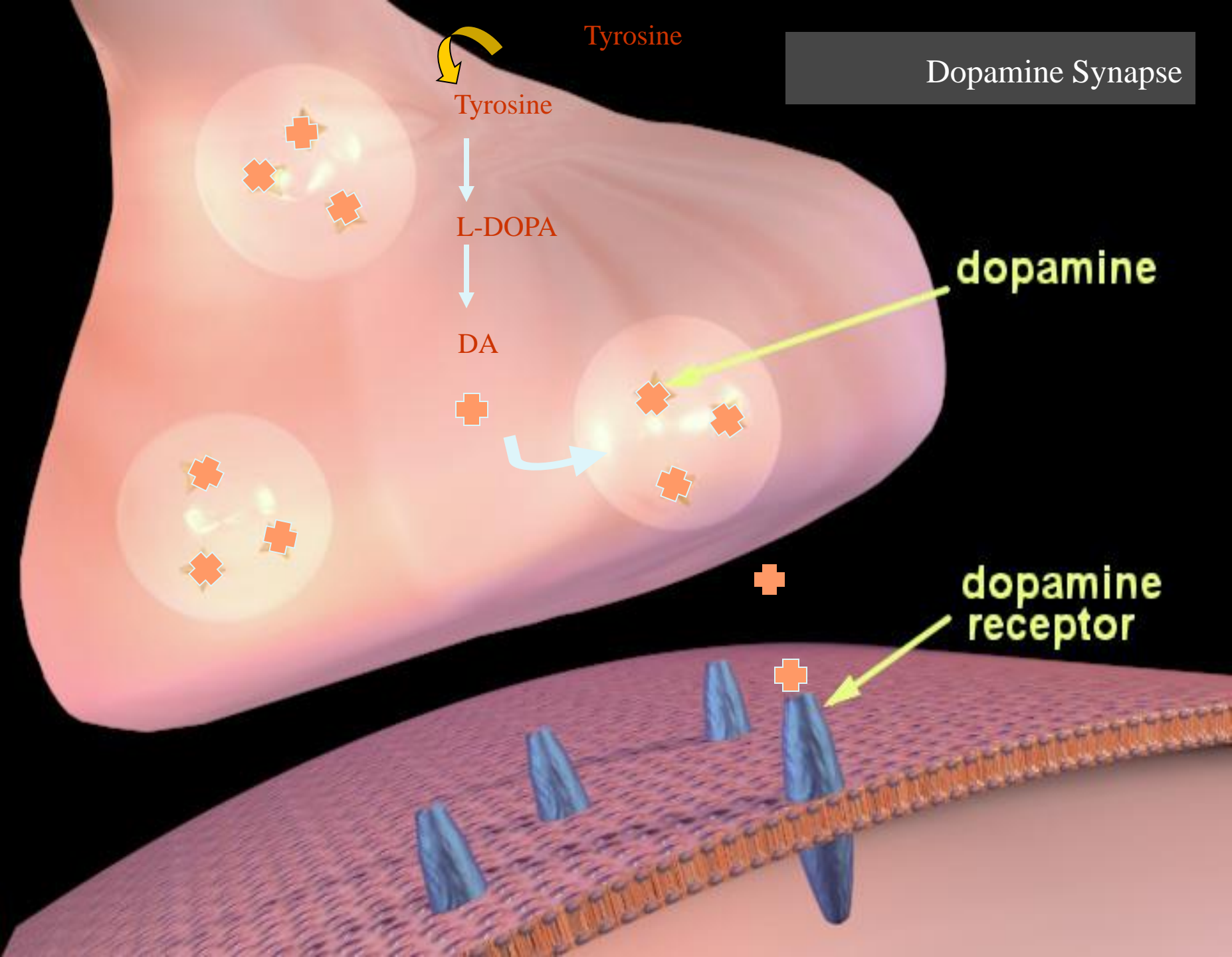
Tyrosine

L-DOPA

DA

dopamine

dopamine receptor



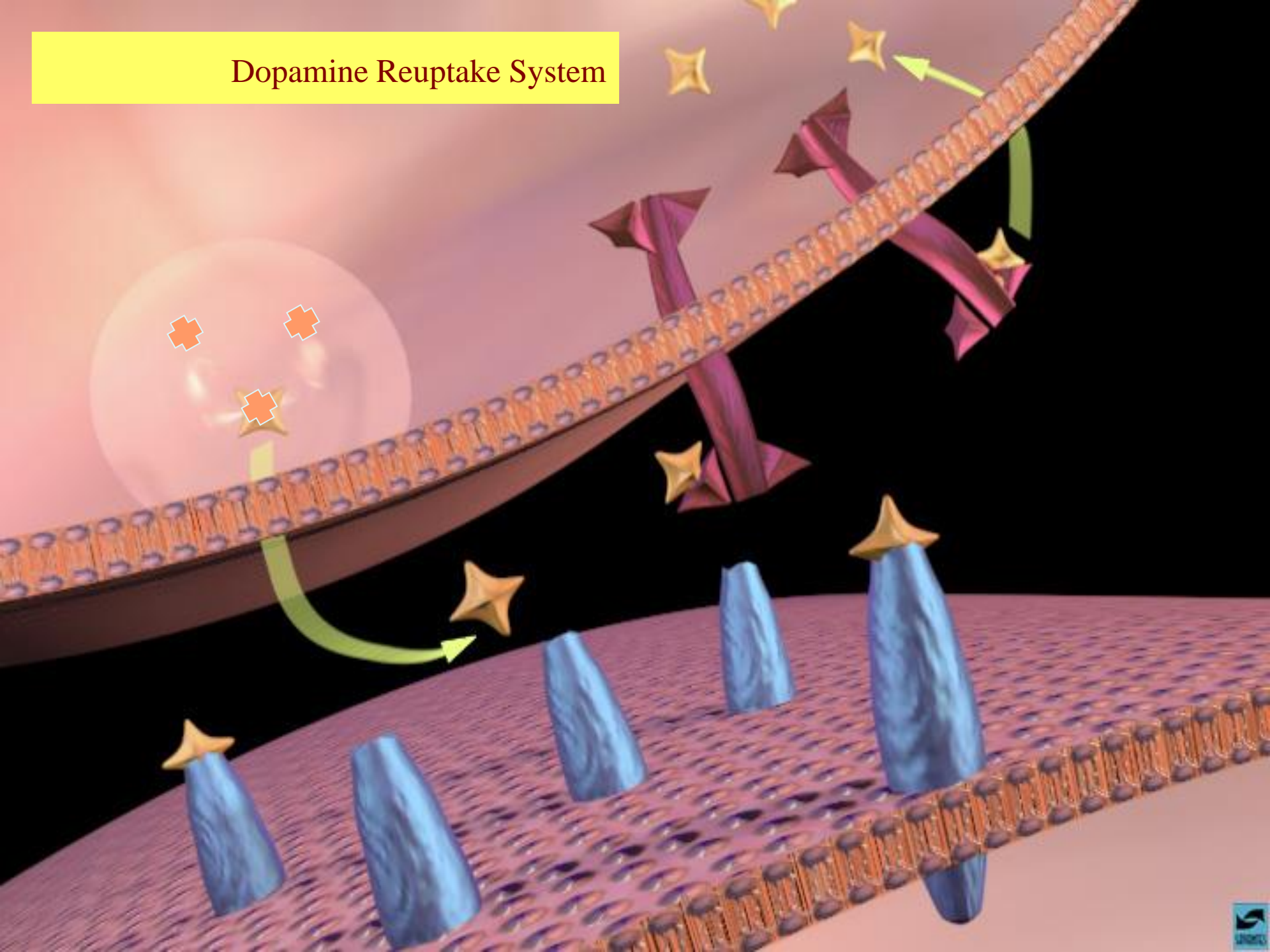
Dopamine System

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

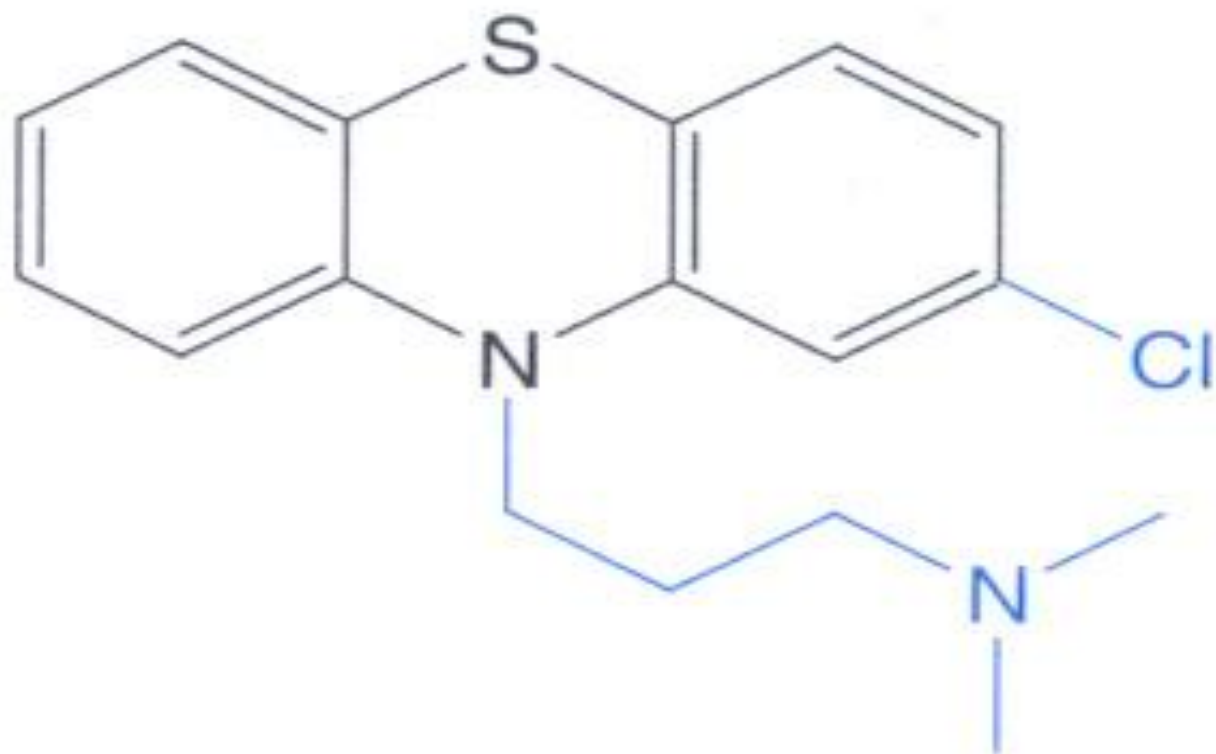
- Haloperidol

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. :

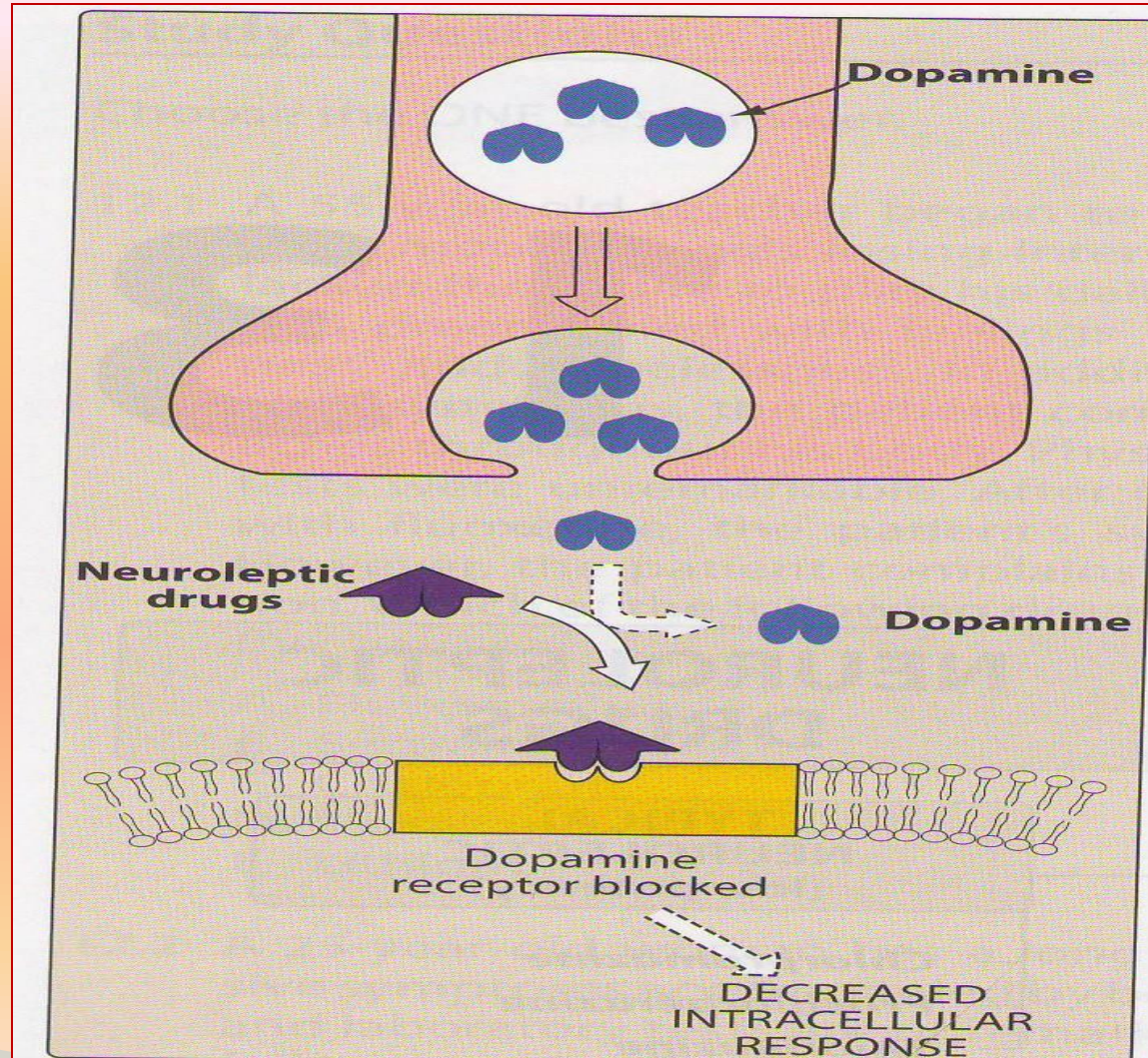
1 – Antipsychotic effect :

- ❖ 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 (5HT₂) & 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 α – adrenergic receptors

Pharmacological Actions (con.)

Other Actions :

1 – Temperature regulation :

May cause lowering of body temperature

Mechanism :

Heat loss as a result of vasodilation

(α - blocking)

Or due to central effect

Other Actions (con.)

2– ECG changes :

Prolongation of QT interval

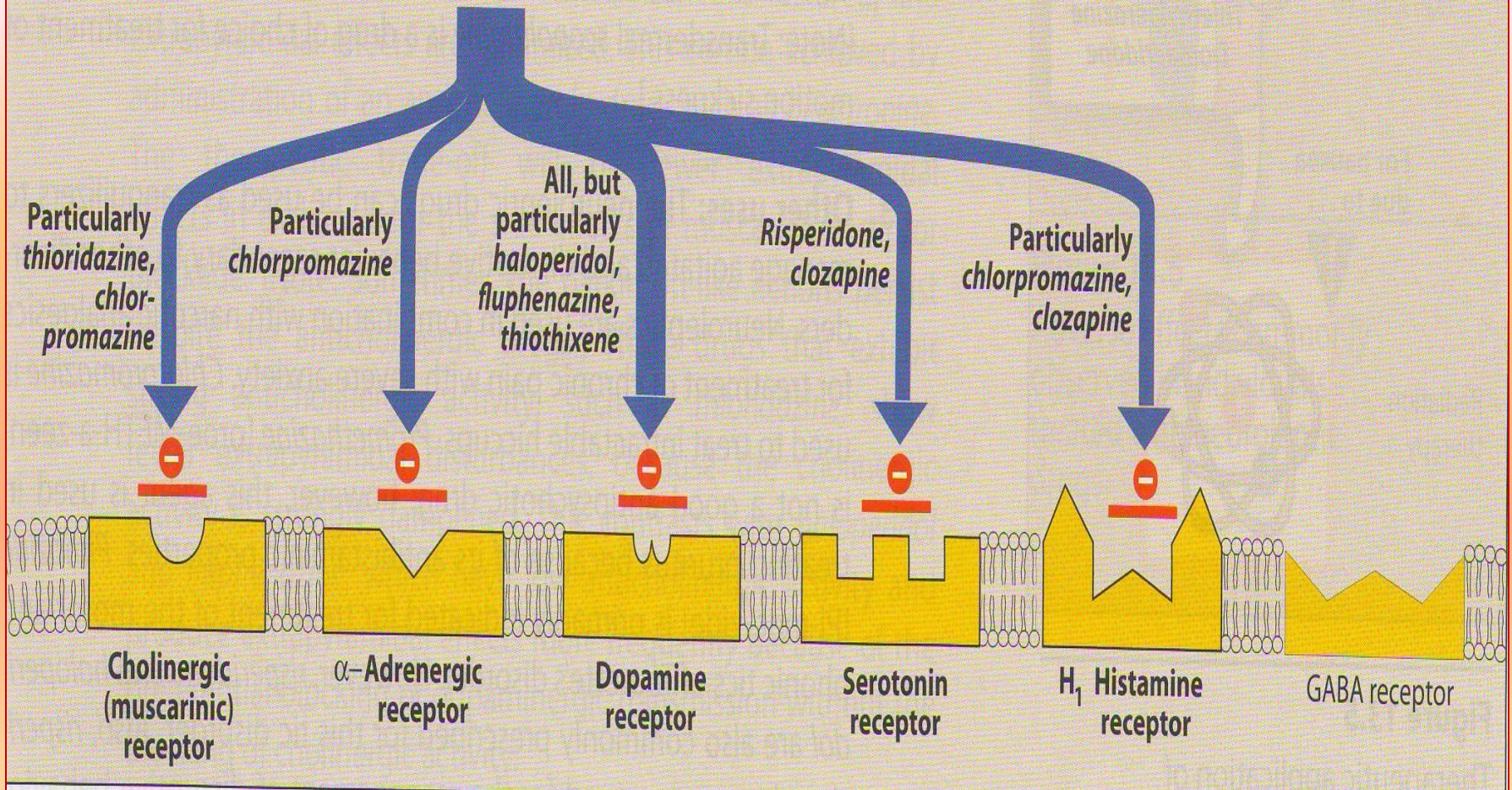
Abnormal configuration of ST– segment & T wave.

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

- **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.**

CLINICAL USES

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

CLOZAPINE

Blocks both D₄ & 5HT₂ receptors

Main adverse effects

Agranulocytosis

Seizures

Myocarditis

Excessive salivation (during sleep)

RISPERIDONE

- ▶ **Blocks D₂ & 5HT₂ receptors**
- ▶ **Main adverse effects**
 - Postural hypotension
 - QT prolongation
 - Weight gain

Contraindicated in patients with long QT interval

OLANZAPINE

- ▶ **Blocks D₁– D₄ & 5HT₂ receptors**
- ▶ **Main adverse effects**
 - **Weight gain**
 - **Sedation**
 - **Flatulence , increased salivation & thirst**
 - **Postural hypotension**

QUETIAPINE

- ▶ Blocks D₁-D₂ & 5HT₂ 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 α -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 & α -adrenergic receptors.
- ▶ The main clinical use is in schizophrenia
- ▶ Examples of atypical drugs includes :
 - Clozapine
 - Risperidone
 - Olanzapine
 - Quetiapine
 - Ziprasidone