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

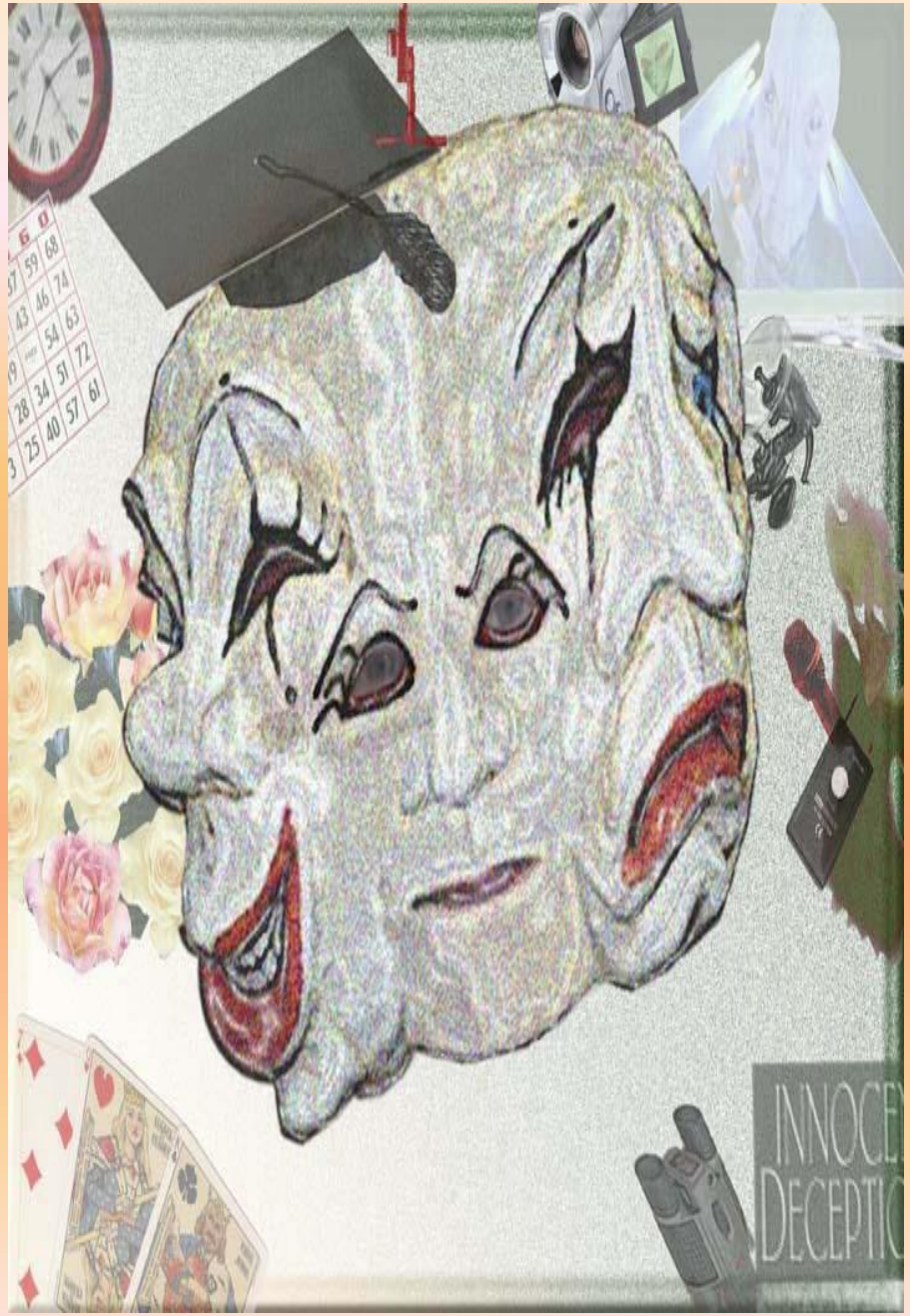
Positive Symptoms

- Hallucinations
- Delusions
- Paranoia

Schizophrenia

Negative Symptoms

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

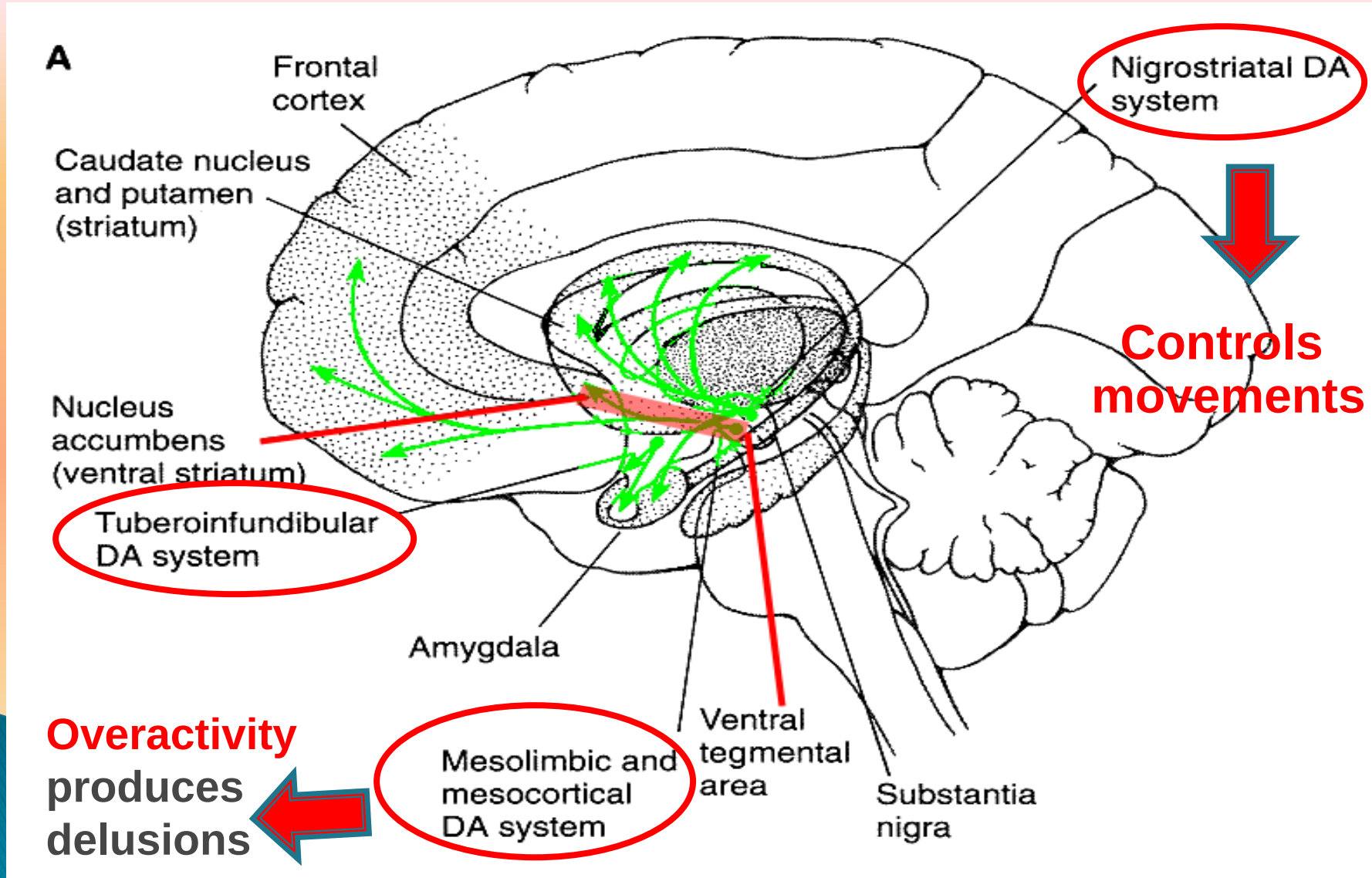

INNOCE
DECEPTI

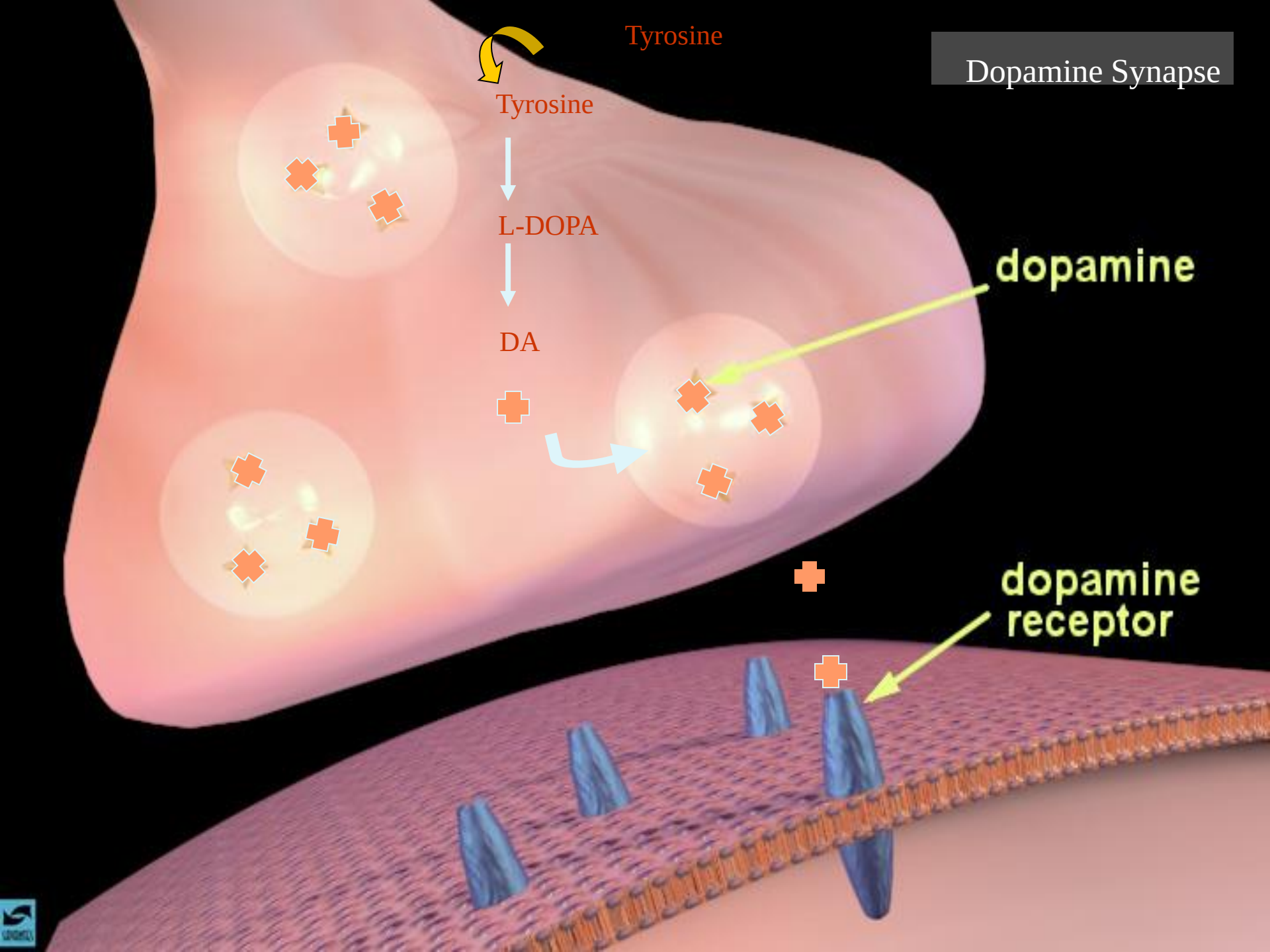
Dopamine System

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)

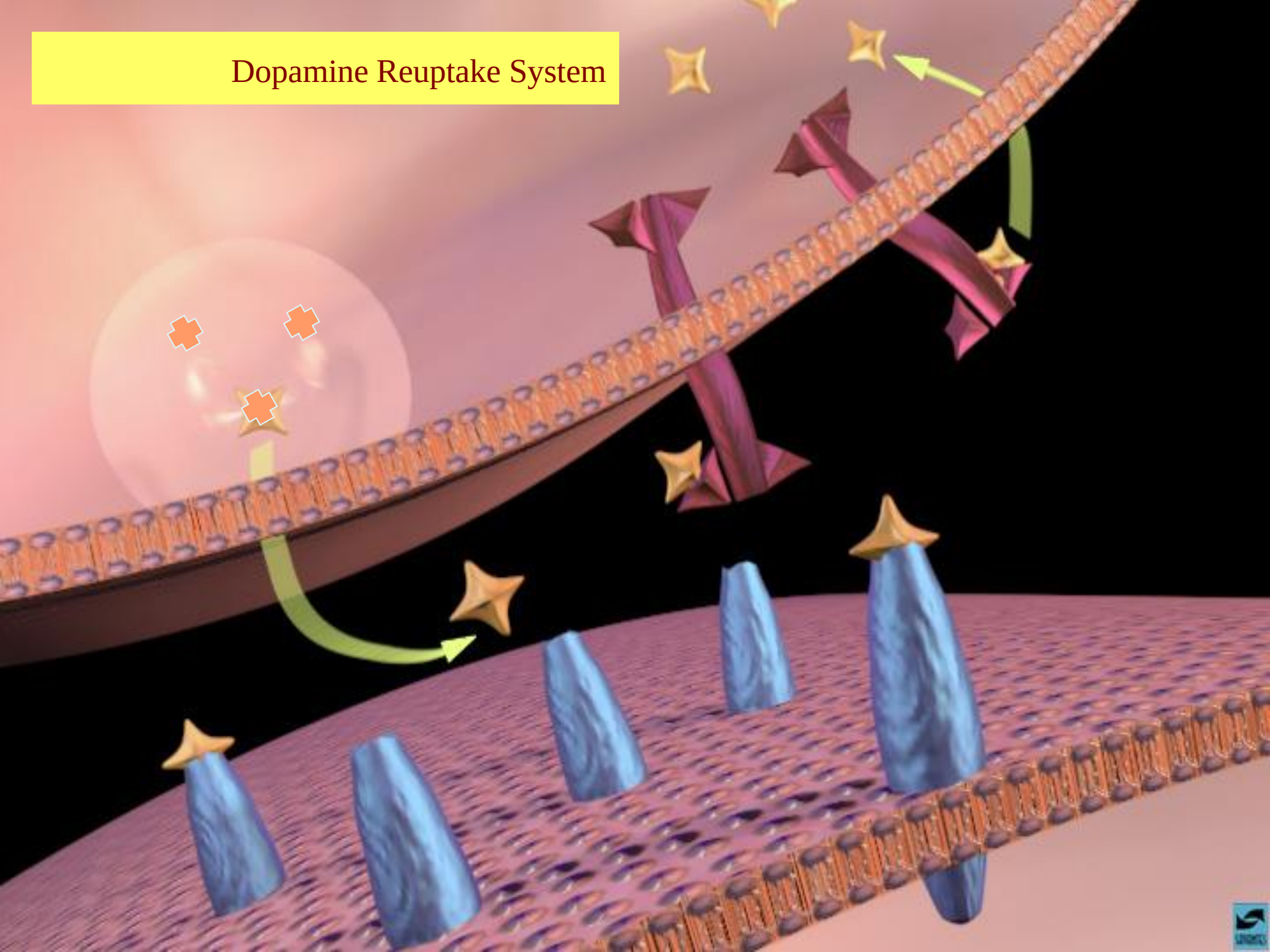
Dopamine Pathways





Dopamine Synapse

Dopamine Reuptake System



Dopamine System

DOPAMINE RECEPTORS

There are at least five subtypes of receptors:

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

Antipsychotic drugs

Classification :

According to chemical structure into :

Typical Antipsychotic Drugs :

1-Phenothiazine derivatives

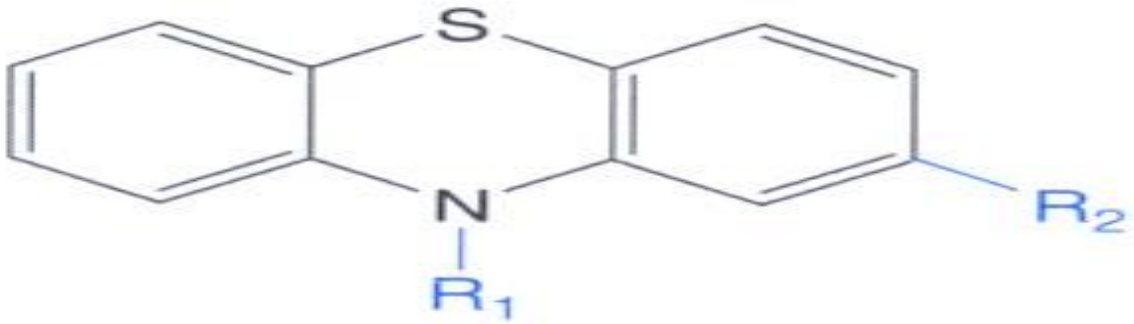
- Chlorpromazine
- Thioridazine

2- Butyrophenones

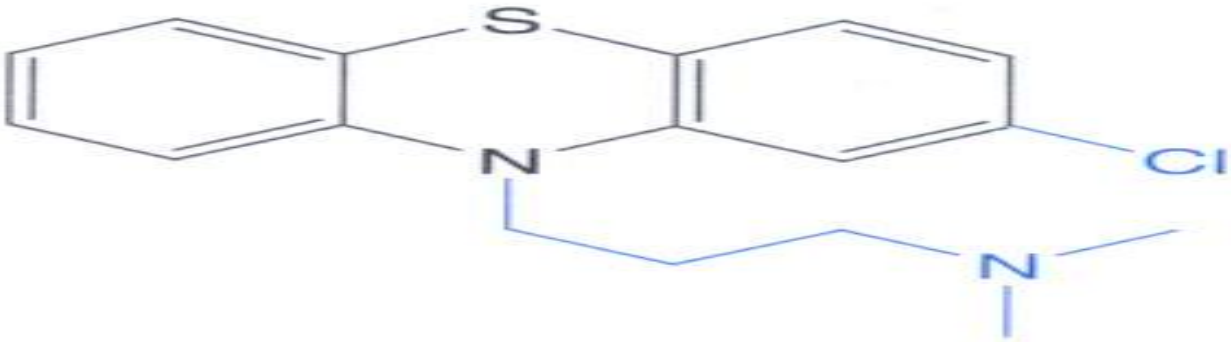
- Haloperidol

3- Thioxanthene

- Thiothixene



Phenothiazine skeleton



Chlorpromazine

Antipsychotic drugs

Classification (cont..)

Atypical Antipsychotic Drugs :

4- Dibenzodiazepines

- Clozapine

5- Benzisoxazoles

- Risperidone

6- Thienobenzodiazepines

- Olanzapine

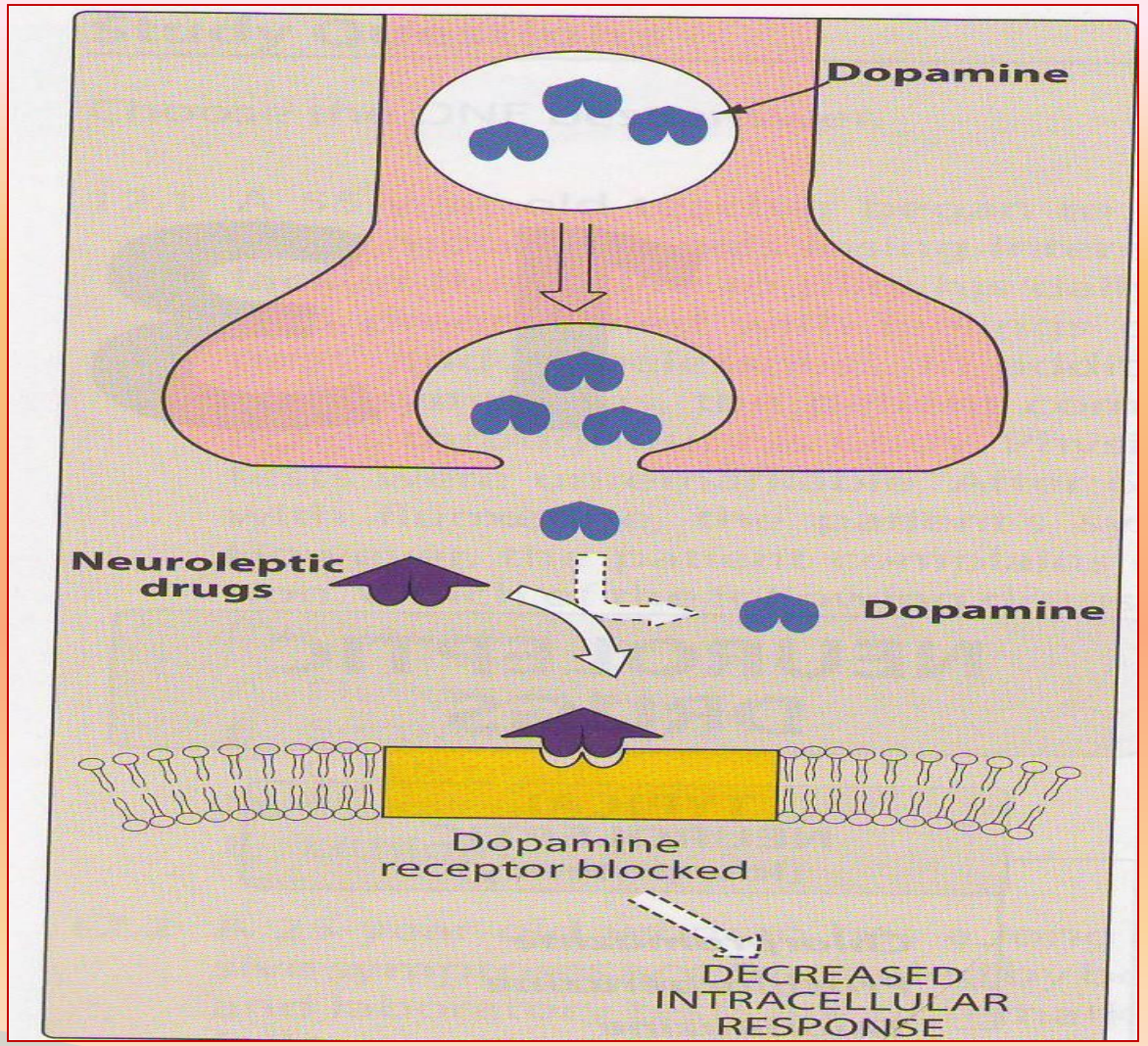
7- Dibenzothiazepines

- Quetiapine

8- Benzisothiazoles

Ziprasidone

Mechanism of Antipsychotic Action



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.

- Atypical drugs exert their antipsychotic action through blocking serotonergic ($5HT_2$) & dopaminergic receptors.

Phrmacological 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 :

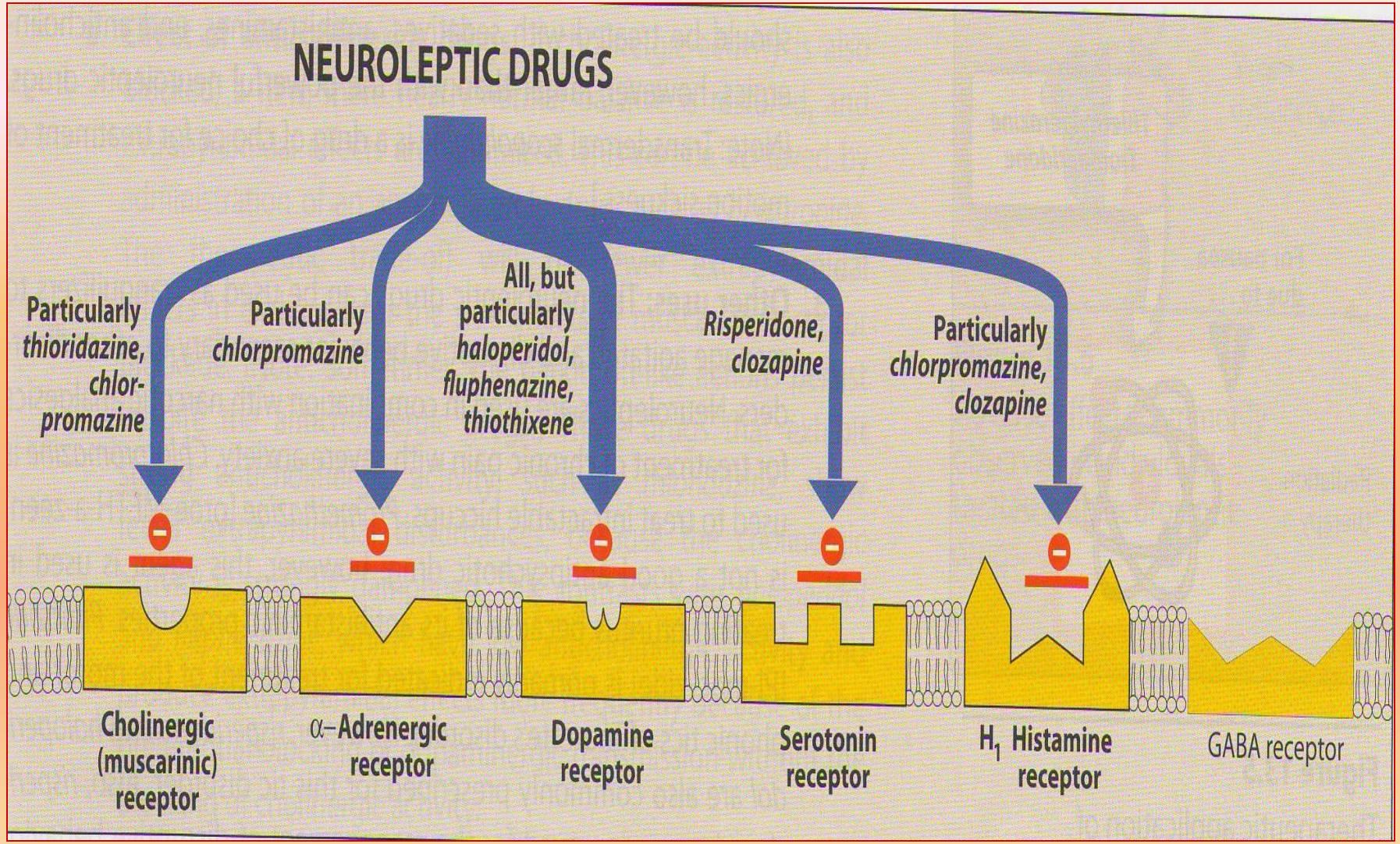
Prolongation of QT interval

Abnormal configuration of ST- segment & T wave.

3- Antihistaminic effect:

Sedation due to H1 receptor blockade

4- Quinidine -like actions


NEUROLEPTIC DRUGS
Particularly thioridazine, chlor-promazine
Particularly chlorpromazine
All, but particularly haloperidol, fluphenazine, thiothixene
Risperidone, clozapine
Particularly chlorpromazine, clozapine
Cholinergic (muscarinic) receptor
α–Adrenergic receptor
Dopamine receptor
Serotonin receptor
H1 Histamine receptor
GABA receptor

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 :

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)

Involuntary movements
of lips, tongue, face, jaws

Adverse Effects (con.)

2- Neuroleptic Malignant Syndrome

- Rare but life threatening.
- Symptoms are muscle rigidity and high fever (clinically similar to anaesthetic malignant hyperthermia).
- Leukocytosis and high fever associated with this syndrome may wrongly suggest an infection.

Adverse Effects (con.)

A.N.S.

- Anticholinergic Effects :
  - Blurred vision
  - Dry mouth
  - Urinary retention
  - Constipation

(Clozapine, Chlorpromazine)

Adverse Effects (con)

- Antiadrenergic Effects :
  - Postural hypotension
  - Impotence
  - Failure of ejaculation

  (Chlopromazine , Thioridazine)

Adverse Effects (con.)

Endocrine Effects :

- Gynecomastia
- Galactorrhoea
- Amenorrhoea

Adverse Effects (con.)

- **Miscellaneous Effects :**

  - Obstructive 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 D_4 & $5HT_2$ receptors

Main adverse effects

- Agranulocytosis
- Seizures
- Myocarditis
- Excessive salivation (during sleep)

RISPERIDONE

- Blocks D_2 & $5HT_2$ receptors

- Main adverse effects
  - Postural hypotension
  - QT prolongation
  - Weight gain

Contraindicated in patients with long QT interval

OLANZAPINE

- Blocks D_1– D_4 & $5HT_2$ receptors
- Main adverse effects
  - Weight gain
  - Sedation
  - Flatulence , increased salivation & thirst
  - Postural hypotension

QUETIAPINE

- Blocks D_1–D_2 & $5HT_2$ receptors
- Main adverse effects
  - Sedation
  - Hypotension
  - Sluggishness
  - Dry mouth
  - 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

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 pathway.**

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