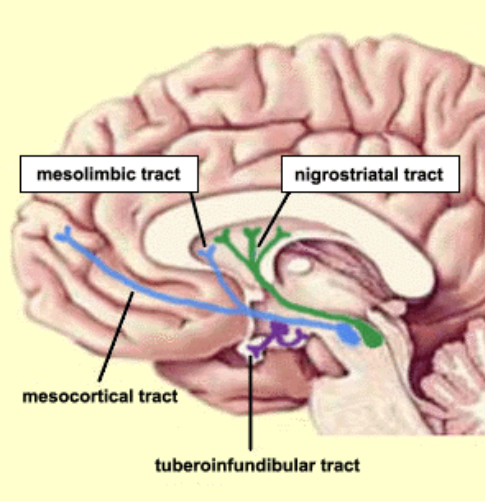
Antipsychotics

The terms **antipsychotic** and **neuroleptic** have been used to denote drugs that have been used to treat schizophrenia and other psychosis.



Dopamine pathways

Revision of dopamine (DA) physiology:

There are 4 important dopaminergic pathways:

- **Mesolimbic-mesocortical pathway:** related to behavior
- **Nigrostriatal pathway:** it is involved in the coordination of voluntary movement
- **Tuberoinfundibular pathway:** dopamine released in this pathway inhibits prolactin secretion
- **Medullary-periventricular pathway:** this system may be involved in eating behavior

Also there are at least 5 dopamine receptors: **D_1, D_2, D_3, D_4, D_5**

Nature of psychosis and schizophrenia

The term psychosis denotes a variety of mental disorders which are:

1. Affected psychoses: mania, depression, maniac-depressive illness (bipolar affective disorder)
2. Schizophrenia

Schizophrenia: it is a mental disorder characterized by a clear sensorium but a marked thinking disturbance.

It has two types of symptoms:

1. **Positive symptoms:** hallucinations, delusions, and paranoia.
2. **Negative symptoms:** social withdrawal, anhedonia (inability to experience pleasure), and emotional blunting.

Pathophysiology:

Two theories are developed to explain the pathophysiology of schizophrenia:

1. **Dopamine theory:** schizophrenia is due to increased dopaminergic activity in the limbic system. This increase is due to:
   - Increased sensitivity or number of dopamine receptors
   - Increased synthesis or release of dopamine
   - Reduced enzymatic destruction of dopamine
2. **Serotonin (5-HT) theory:** serotonin deficiency might have been the cause of schizophrenia. This theory is based on the observation that LSD (5-HT antagonist) produces hallucinations.

Basic pharmacology of antipsychotic agents

CHEMICAL TYPES:

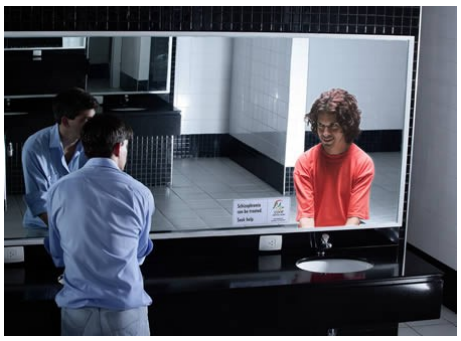
Antipsychotic drugs are divided to 2 groups:

1. **Typical antipsychotics:** which are divided into 3 groups based on chemical structure:

- **Phenothiazine derivatives:** chlorpromazine and thioridazine; They are the least potent drugs
- **Thioxanthene derivatives:** thiothixene. They are slightly less potent than pehnothiazines.
- **Butyrophenone derivatives:** haloperidol. They are more potent.

2. **Atypical antipsychotics:** the newer drugs. They are divided to many groups for example:

- **Dibenzodiazepines: (**clozapine**)**
- **Benzisoxazoles:** (risperidone)
- **Thienobenzodiazepines** (olanzapine)
- **Dibenzothiazepines** (Quetiapine)



Hallucination: one of the symptoms

Differences among antipsychotic drugs:
Typical antipshycotics acts on D_2 receptors. In this case binding affinity is correlated with clinical antipsychotic and extrapyramidal potency.
Atypical antipsychotics act on 5-HT receptors and DA receptors.
Both of these drugs can also act on histamine, α, and muscarinic receptors

Pharmacokinetics:

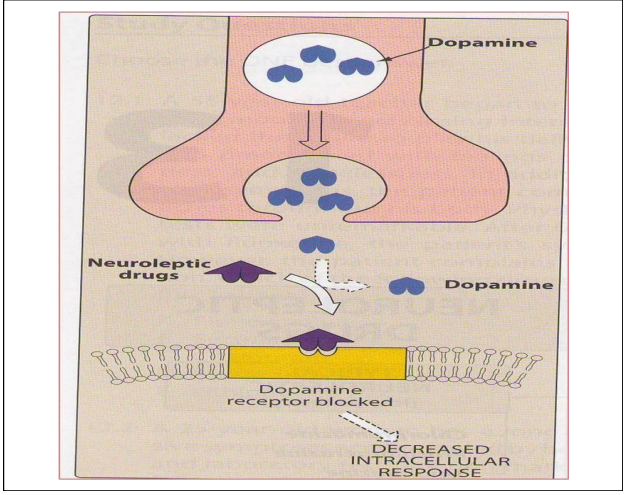
Most of antipsychotic drugs are incompletely absorped. Furthermore, many of them undergo extensive first-pass metabolism. They tend to have a large volume of distribution. Also, they are highly bound to plasma protein. They are lipid-soluble and they are excreted by the kidneys.
Metabolism: most of the drugs have complicated metabolism. We have here two examples:

- Chlorpromazine: has about sixty different metabolites some of which are considered active metabolites. These metabolites may still be excreted in urine after months of stopping the drug.
- Thioridazine: its metabolite is **mesoridazine** which is more potent than the parent compound.

Pharmacological effects:

A. Dopaminergic systems:

- Antipsychotic drugs produce emotional quieting and psychomotor slowing and decrease hallucinations, delusions, and agitation. This is caused by blockade of D_2 receptors in the mesolimbic system.. Atypical drugs exerts their action by blocking 5-HT and DA receptors
- They cause involuntary movements such as tremors, parkinsonism, and tardive kinesia by blocking DA in nigrostriatal pathway (extrapyramidal toxicity).
- They block DA in tuberoinfundibular pathway and increase peripheral conversion of androgens to estrogens which leads to galactorrhea, amenorrhea, gynnecomastia, increased libido in women, decreased libido in men, and infertility.
- Also, changes in weight and eating behavior occurring in the light of the blockade to the medullary-periventricular pathway. (clozapine and olanzapine cause weight gain)



Antipsychotics action on DA receptors

B. Psychological Effects:

Antipsychotic drugs cause unpleasant sensation effects in nonpsychotic individuals eg, sleepiness, restlessness, and autonomic effects.

Psychotic individuals show improvement in their performance.

C. EEG Effects:

Antipsychotics produce shifts in EEG frequencies, usually slowing them and increasing their synchronization.

D. Cardiovascular Effects:

- In general, antipsychotics decrease mean arterial pressure, peripheral resistance, and stroke volume. They increase heart rate.
- ECG changes: prolongation of QT interval and abnormal configuration of ST segment & T wave (**ziprasidone** carries the greatest risk)

E. Autonomic Effects:

- Blurred vision, dry mouth, urinary retention, and constipation are caused by antimuscarinic action. (clozapine and chlorpromazine)
- Postural hypotension, impotence, failure of ejactulation are caused by antiadrenergic action. (thioridazine and chlorpromazine)

F. Other Effects:

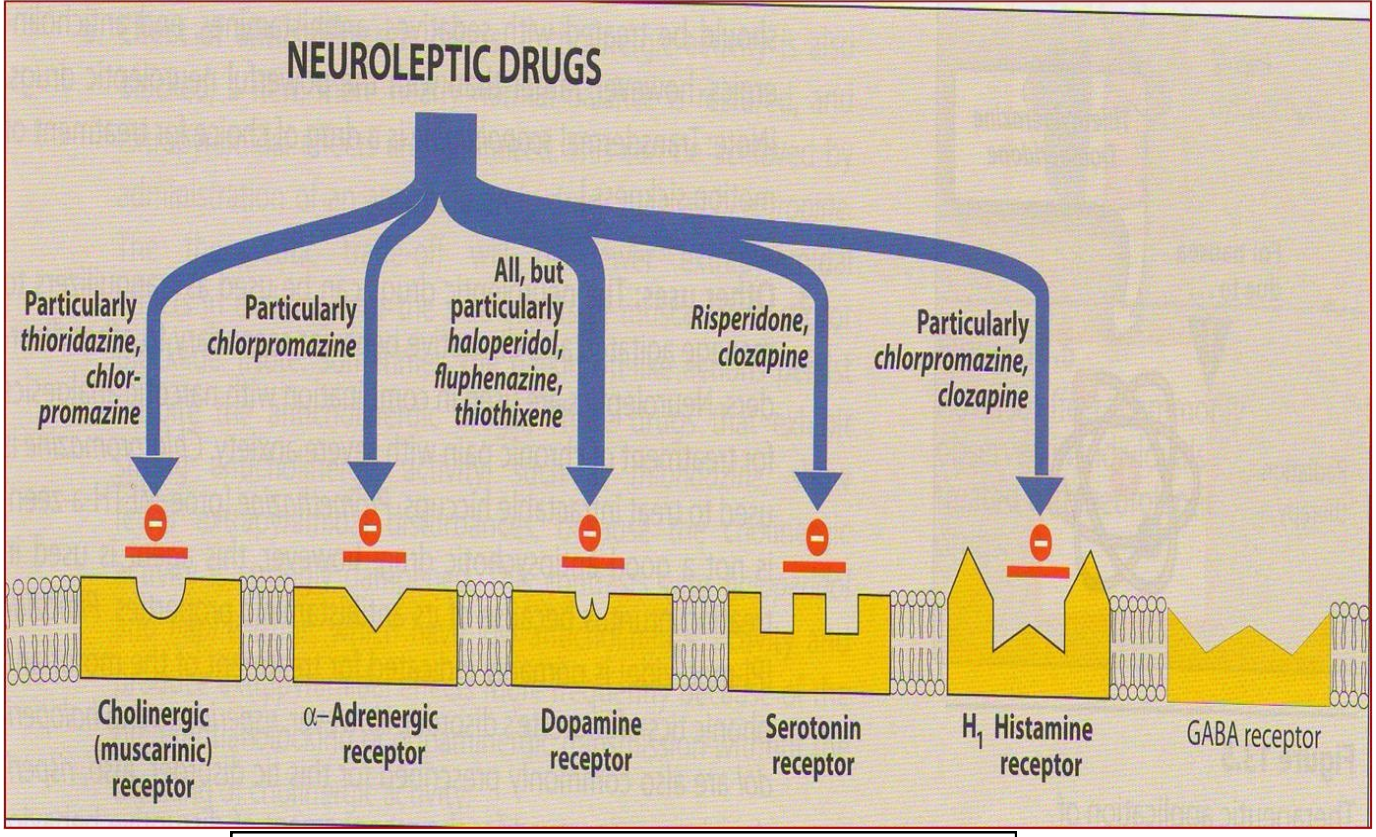
- Temperature regulation: they lower body temperature by α receptors blocking (vasodilation) or central effect.
- They cause sedation by blocking histamine receptors.
- They may cause quinidine-like action.
- They are effective against drug-disease induced vomiting (by blocking DA receptors in chemoreceptor triggering zone (CTZ).

Clinical pharmacology of antipsychotic agents

INDICATIONS:

A. Psychiatric Indications:

- Schizophrenia is the primary indication.
- They are also indicated in schizoaffective disorders.
- The manic phase in bipolar affective disorder
- Olanzapine can be used in acute mania. As mania subsides atypical antipsychotic is used as maintenance treatment.
- Other indications: tourette's syndrome, disturbed vehavior in patients with Alzheimer's disease, psychotic depression.
- They are not indicated for treatment of withdrawal syndromes.



This figure illustrates antipsychotic receptor affinity

Drug	D_2/5-HT_{2A} Ratio[1]	Clinical Potency	Extrapyramidal Toxicity	Sedative Action	Hypotensive Actions
Chlorpromazine	High	Low	Medium	High	High
Fluphenazine	High	High	High	Low	Very low
Thiothixene	Very high	High	Medium	Medium	Medium
Haloperidol	Medium	High	Very high	Low	Very low
Clozapine	Very low	Medium	Very low	Low	Medium
Risperidone	Very low	High	Low[2]	Low	Low
Olanzapine	Low	High	Very low	Medium	Low
Quetiapine	Low	Low	Very low	Medium	Low to medium
Ziprasidone	Low	Medium	Very low	Low	Very low
Aripiprazole	Medium	High	Very low	Very low	Low

[1] Refers to affinity for 5-HT_{2A} receptors.

B. Nonpsychiatric Indications:

- Most older antiphychotics, except thioridazine, have a strong aneiemetic effect. Pro-chlorperazine and benzquinamide are promoted solely as antiemetics.
- Phenothiazines have been used to relieve pruritus
- Promethazine have been used as preoperative sedative
- Butyrophenone droperidol is used in nueroleptanesthesia

Drug choice:

- New antipsychotic have been shown to be more effective for treating negative symptoms
- Older drugs have parenteral preparations (e.g. fluphenazine and haloperidol) and they are cheap.
- The best guide for selecting a drug is the patient's past responses to these drugs.
- Clozapine is the choice for patients who have become refractory to other drugs.

Adverse effects:

Note: these adverse effects that were not mentioned in pharmacological effects section

A. Behavioral Effects:

- Peudodepression that may be due to drug-induced akinesia (treated by antiparkinsonisms)
- Toxic-confusional states occurs with high doses of antipsychotics with antimuscarinic actions.

B. Neurological effects:

- Sedation, drowsiness fatigue (caused by haloperidol and risperidone)
- **Parkinson's syndrome, akathisia** (uncontrollable restlessness), and **acute dystonic reactions** (spastic retrocollis or torticollis): they're treated by withdrawal of insulting drug, antiparknisonism drugs (not levodopa), or diphenhydramine.
- **Tardive dyskinesia:** abnormal choroatheroid movments. Treated by:

First step: discontinue or reduce the dose or switch to atypical agent.
Second step: eliminate all drugs with central anticholinergic action.
Final step: diazepam

- **Seizures:** occur in 2-5% of patients treated with clozapine.

C. Toxic or Allergic Reactions:

- Cholestatic jaundice and skin eruptions occur with high potency antipsychotics
- Clozapine causes reversible agranulocytosis in 1-2% of patients (need weekly monitor)

D. Ocular Complications:

- Deposits in the anterior portion of the eye is a complication of chlorpromazine.
- Thioridzine is the only antipsychotic that causes retinal deposits.

E. Cardiac Toxicity:

- Thioridzine causes minor reversible abnormalities of T wave. Overdoses are associated with ventricular arrhythmia, cardiac conduction block, sudden death. Tricyclic antidepressents should be combined with great care.
- Ziparosidone should not be combined with thioridazine, pimozide, and quinidine.

F. Neuroleptic malignant syndrome:

It's a rare life-threatening disorder. The symptoms are muscle rigidity, autonomic instability, altered blood pressure and pulse rate, and fever. Stress leukocytosis and high fever associated may suggest an infectious process. Treated by antiparkinsonisms, muscle relaxants (diazepam, dantrolene, dopamine agonists), and cooling by physical measures.

Specific adverse effects:

Drug	Adverse effects
clozapine	Myocarditis and excessive salivation
risperidone	Weight gain
olanzapine	Weight gain, sedation, flatulence, increase salivation, joint stiffness, and dental pain
Quetiapine	Sedation, leukopenia–neutropenia, and hyperglycemia