

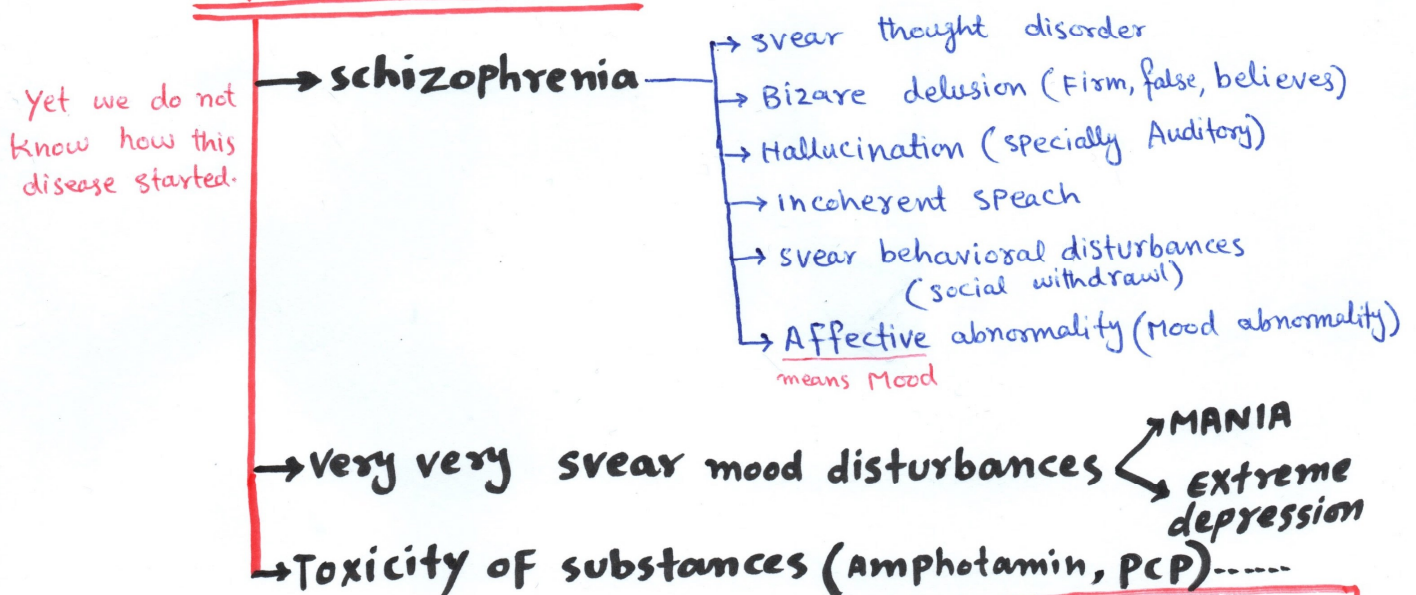
# Anti Psychotic Drugs

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**Psychosis:** Most severe mental disturbances in which patient loss contact with Reality. Eg: Schizophrenia.....

**Neurosis:** Mild group of mental disorders in which patient have contact with Reality. Eg: OCD, Anxiety.....

## Psychosis Consist of



antipsychotic drugs only decrease the symptoms, & do not alter the pathogenic process

- Schizophrenia is common as Diabetes mellitus.
  - Most of the time this disease start in Adolescence & affect about 1% of global population.
  - There is no cure for psychotic diseases
  - some of schizophrenia patient develop **KATATONIA** (A condition in which patient develop any posture, & remain in that posture for long time)
    - Mania
    - Extreme depression
- Psychosis occur in schizophrenia, v.v. severe mood disturbances, and Toxicity of drugs (Amphetamine, PCP). \*in case of drug toxicity patient symptoms reverse after discontinue of drug.

# Symptoms of schizophrenia

There are 2 types of symptoms

(1) Positive symptoms: Those symptoms which are added to the patient personality (e.g: delusion, Hallucination ----)



(2) Negative symptoms: Those symptoms which are eliminated or deleted from patient personality (e.g: social withdrawal, ↓ Motivational, <sup>behavior</sup> loss of display of emotions)

## ANTIpsychotic DRUGS

**TYPICAL**  
(discovered first)  
Typical drugs treat positive symptoms

**DETAILED LATER**

**ATYPICAL**  
has ↓ sideeffects  
Atypical Mostly cover positive as well as negative symptoms.  
\* [These drugs are highly expensive]

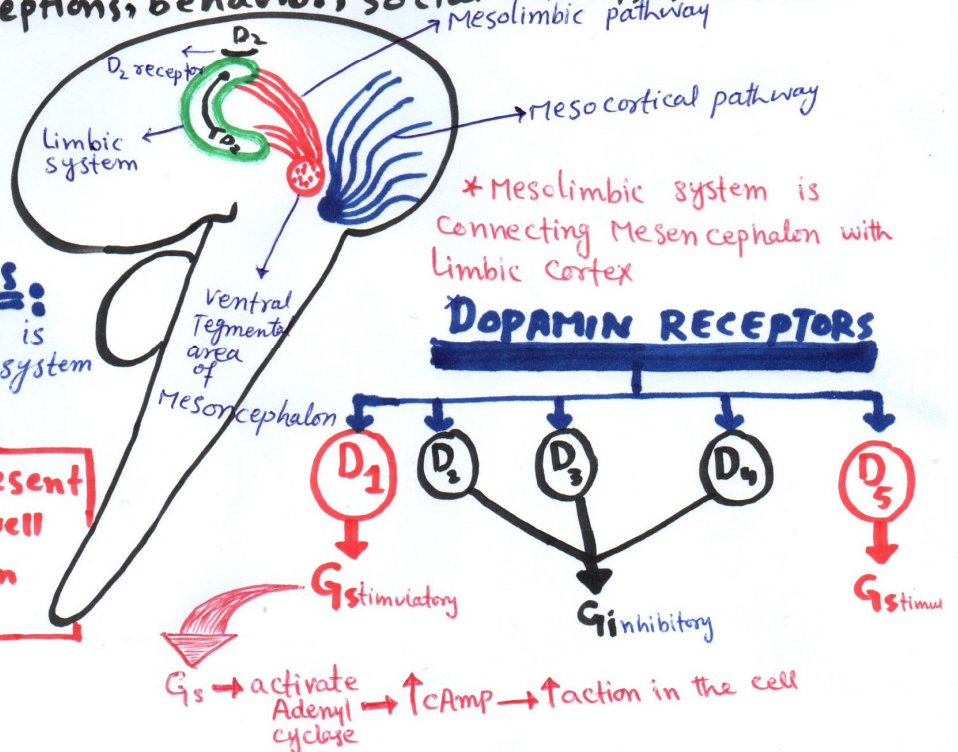
according to some theories psychosis is due to increased Dopaminergic activity in the CNS. which is concerned with thoughts perceptions, behavior, social activity, & Motivation.

Important Dopaminergic system are:  
\* Limbic system &  
\* Pre frontal lobe

### Dopamin hypothesis

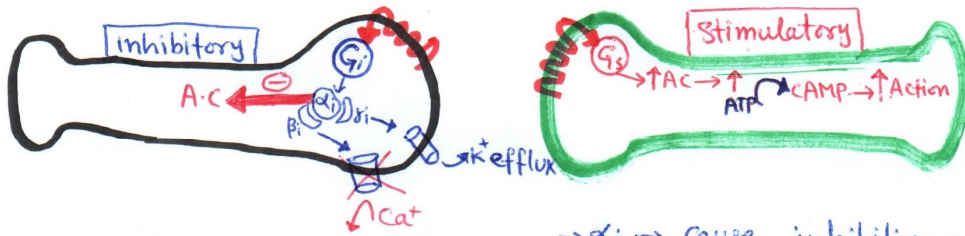
Excess dopamin which is produced by mesolimbic system cause positive symptoms.

**D<sub>2</sub> receptors are present presynaptically as well as postsynaptically in Limbic system**





presynaptic & Post synaptic neuron of Limbic system.



all Dopamin receptors are 7 Pass receptor  
↓ action within the cell

So No TAP change to CAMP

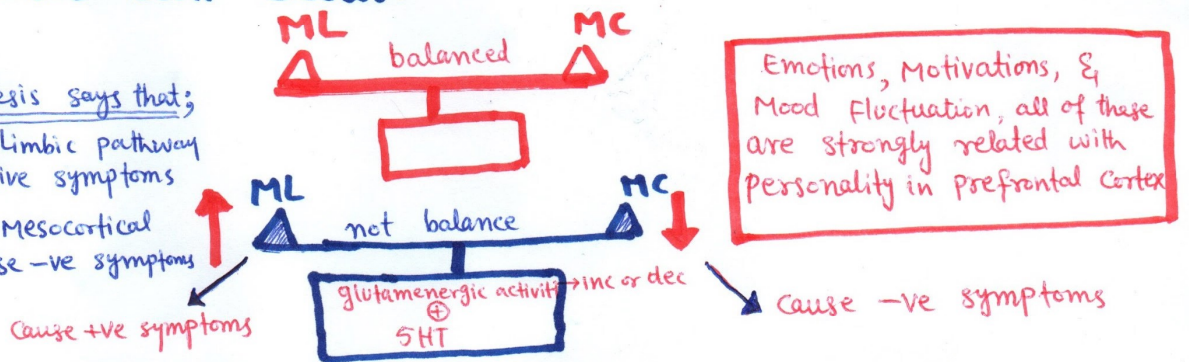
Gi has 3 components —

- αi ⇒ Cause inhibition of Adenyl cyclase
- βi ⇒ block Ca<sup>2+</sup> channel, so Ca<sup>2+</sup> not enter to cell
- γi ⇒ opens K<sup>+</sup> channel, so alot of K<sup>+</sup> loss due to these above changes, cell become more -ve, & not excited.

according to new concept; There is a balance b/w Mesolimbic (ML) pathway & Mesocortical (MC) pathway. If this balance is altered due to any reason Psychosis will occur.

New hypothesis says that;

- ① ↑ activity in Limbic pathway Cause positive symptoms
- ② ↓ activity in Mesocortical pathway Cause -ve symptoms



classical antipsychotic drugs are dopamenergic, they are D<sub>2</sub> sensitive.

\* Typical antipsychotic drugs block D<sub>2</sub> & block mesolimbic pathway & Cure +ve symptoms.

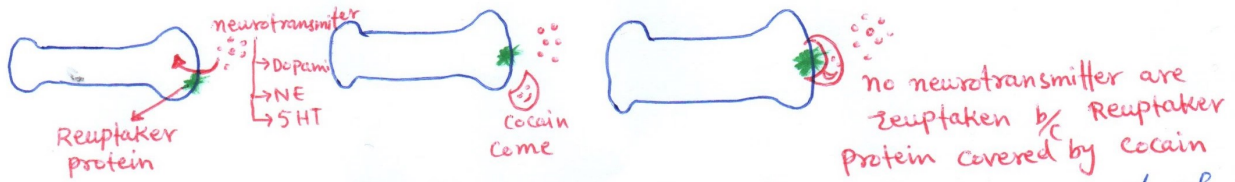
### Dopamin hypothesis (How psychosis occur)

- D<sub>2</sub> receptor blocker
- L-Dopa, Cocain, Amphotamin
- patient treated by antipsychotic drugs; Living or postpartum → in their mesolimbic system there is ↑ D<sub>2</sub> receptor
- ↓ Homovanilic Acid in (Blood, CSF, Urin)  
↳ it is a breakdown of dopamin

Those drugs which increase dopamin level high, they Cause psychosis

## How Cocain work

normally neuron release monoamine neurotransmitters, and 80% of these neurotransmitters are reuptaken. COCAIN bind with reuptaker protein, so such neurotransmitters are not uptaken, so ↑ amount of neurotransmitter at synapses.



- \* So if Dopamin hypothesis was true than Excessive amount of Cocain also produce psychosis.
- \* Amphetamine increase release of dopamin, Nor epinephrin & 5HT, so these high amount of NE & 5HT cause psychosis.

## ANTIPSYCHOTIC DRUGS

### TYPICAL

These are only  $D_2$  antagonist  
These drugs bind strongly & for longer duration  
(have stronger affinity for receptor)

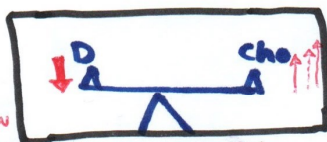
### ATYPICAL

These are mainly 5HT antagonist & (serotonin)  
Weakly  $D_2$  antagonist  
These drugs binds in mild way & for shorter duration  
(They have less affinity for receptor)

5 Hydroxy Tryptamine 2

NOTE: All Antipsychotic drugs are  $D_2$  antagonist.

in basal ganglia there is balance b/w

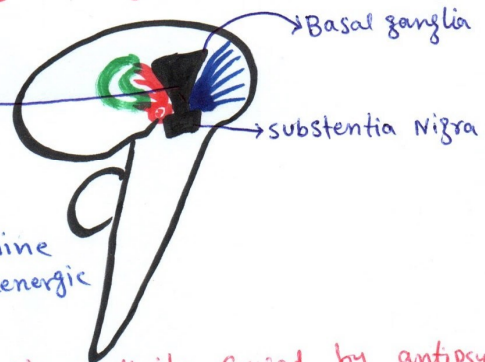


Dopamenergic and cholinergic activity

Basal ganglia

antipsychotic drugs decrease dopamine while cho are unapposed, so cholinergic activity increases.

Nigrostriatal pathway



The imbalance B/w Dopamenergic & cholinergic activity caused by antipsychotic drugs ~~also~~ produce important sideeffects called **EXTRA PYRAMIDAL SIDE EFFECTS (E.P.S.E)**

Key Point: ATYPICAL does not binds strongly with Dopamin receptor, so does not disturb nigrostriatal pathway, so don't produce (E.P.S.E).

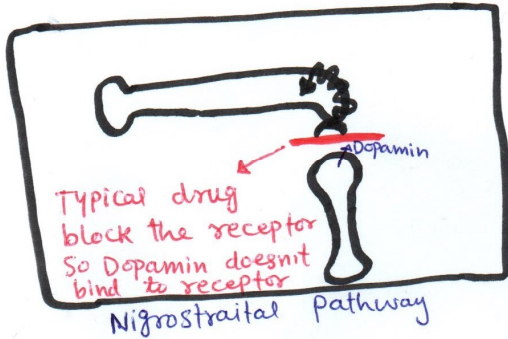
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# RELEASE OF DOPAMIN

**TONIC RELEASE**  
(when nerve ending is not stimulated by Action potential)

**LARGE AMOUNT OF RELEASE**  
(when Action potential comes to nerve ending, there is a surge of Dopamin release)



Typical drug binds strongly with receptor, so if even Tonic or surge of Dopamin comes it will not remove the Drug from receptor

But as Atypical drugs binds only transiently & slowly; so even when dopamin surge occurs it will remove such drug from receptor.

\* In Case of psychosis presently it is believed that Excessive activity is due to Tonic release of Dopamin

Tonic activity is blocked by Typical and ATypical both drugs. its means that typical & Atypical both are antipsychotic.

⇒ Typical drugs block  $D_2$  receptor on both Nigrostriatal & Mesolimbic pathway.

⇒ ATypical drugs also bind with  $D_2$  receptor but transiently & slowly.

\* psychosis is due to increased Tonic dopamenergic system in mesolimbic system.

## EXTRA PYRAMIDAL SIDE EFFECTS

These occur due to decrease Dopamin activity ↓D

→ **Dystonias** → some patient when given antipsychotic drugs within few hours they develop dystonia (very severe spastic contraction in postural muscles) (within few hours)

→ **AKINESIA** (Parkinson like syndrome) ⇒ within few days — weeks.

Akinesia ⇒ Difficulty in initiating purposeful movements

→ **AKATHESIA** ⇒ (Motor restless without anger) e.g: Torticollis (W<sup>o</sup> — M<sup>o</sup>)

This occur due to increase Dopamin activity ↑D

→ **TARDIVE DYSKINESIA** → (Involuntary unstopable movements of orofacial muscles) (M<sup>o</sup> — Y<sup>o</sup>) mostly this occur in elderly ♀ (slow Dysregulated Movements) (occur in late treatment) (S)





## other dopaminergic system

Normally Tubero infundibular system release dopamine, & keeps lactotropes inhibited.

Typical antipsychotic drugs bind with  $D_2$  receptor on lactotropes & block that receptor, so in this way prolactine level increases.

this high level of prolactine cause abnormality in:

♀ ⇒ galactorrhea,

↓ FSH & LH ⇒ ↓ ovary maturation, & No corpus luteum eventually Amenorrhoea develops ⇒ infertile

Libido in both ♂ & ♀ depends on Androgens

In ♂ → Adrenal cortex  
→ Testes

In ♀ → Adrenal cortex

In ♀ the libido doesn't decrease, but such ♀ are not become pregnant.

But pregnancy test may show (False +ve) b/c of ↑ prolactin

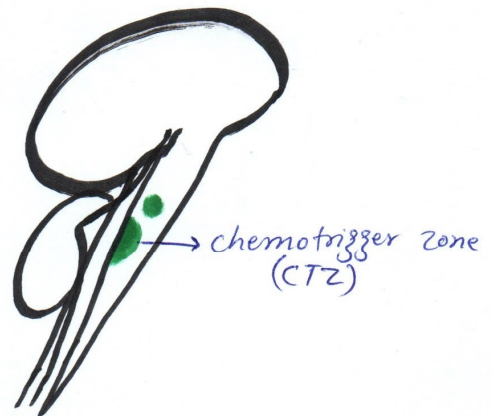
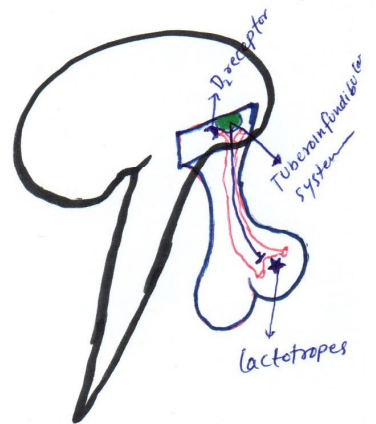
If ♂ with schizophrenia is on antipsychotic drugs he develop

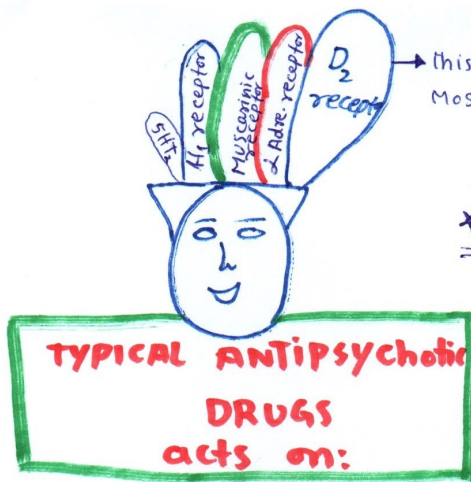
- ① galactouria
- ② ↓ Libido
- ③ weight gain
- ④ Gynecomastia
- ⑤ infertility

In Floor of 4th ventricle there is a Chemotrigger Zone, This zone has a lot of Dopaminergic neurons.

When this zone is stimulated by some Noxious substances it cause: Nausea & Vomitting

antipsychotic drugs block that  $D_2$  receptor & inhibit nausea & vomitting, so these drugs are used as anti emetic.





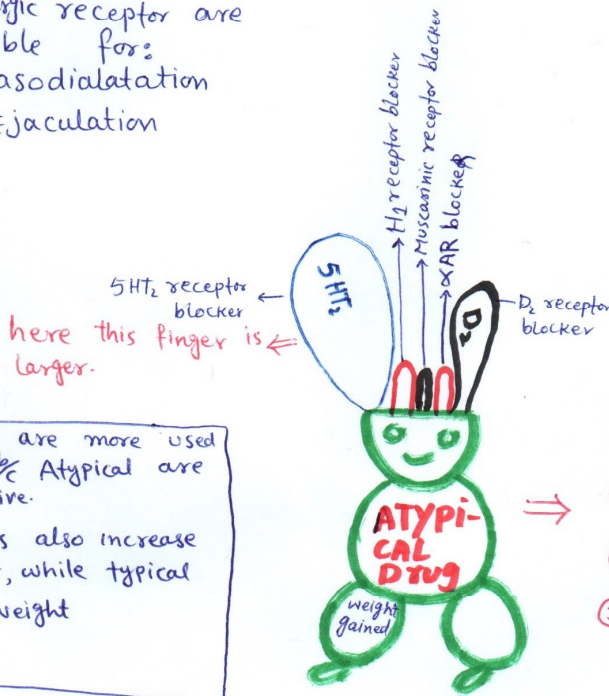
this finger is larger its means these drugs Mostly acts on D<sub>2</sub> receptor.

\* Typical antipsychotic drugs block the following receptors:

- ① D<sub>2</sub> receptor when blocked
  - good effects
    - ↳ antipsychotic
    - ↳ Antiemetic
  - Bad effects
    - ↳ ↑ EPSE
    - ↳ ↑ prolactin
- ② α Adrenergic receptor blocked due to which:
  - ↳ vaso constriction &
  - ↳ failure to ejaculation occur
- ③ Muscarinic receptor blocked: cause
  - ↳ Confusion
  - ↳ Forgetfulness
  - ↳ fecal retention
  - ↳ urinary retention
- ④ H<sub>1</sub> receptor block cause:
  - ↳ sedation

α Adrenergic receptor are Responsible for:

- ① vasodilatation
- ② Ejaculation

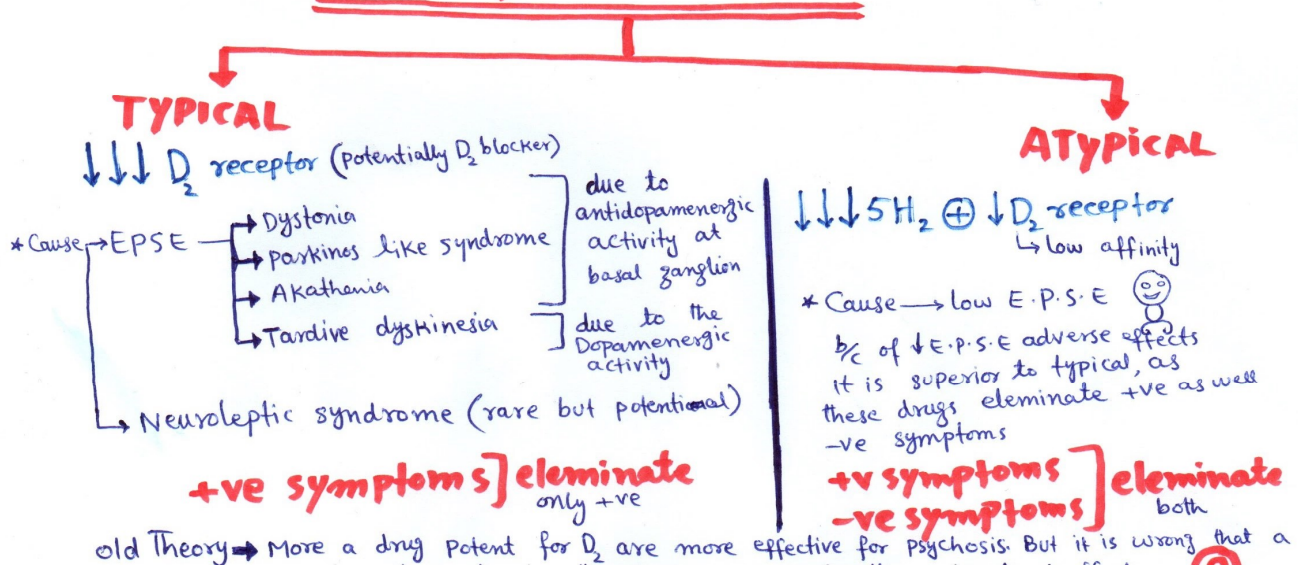


\* Typical drugs are more used than atypical b/c Atypical are much EXPENSIVE.

\* Atypical drugs also increase body weight, while typical doesn't ↑ weight

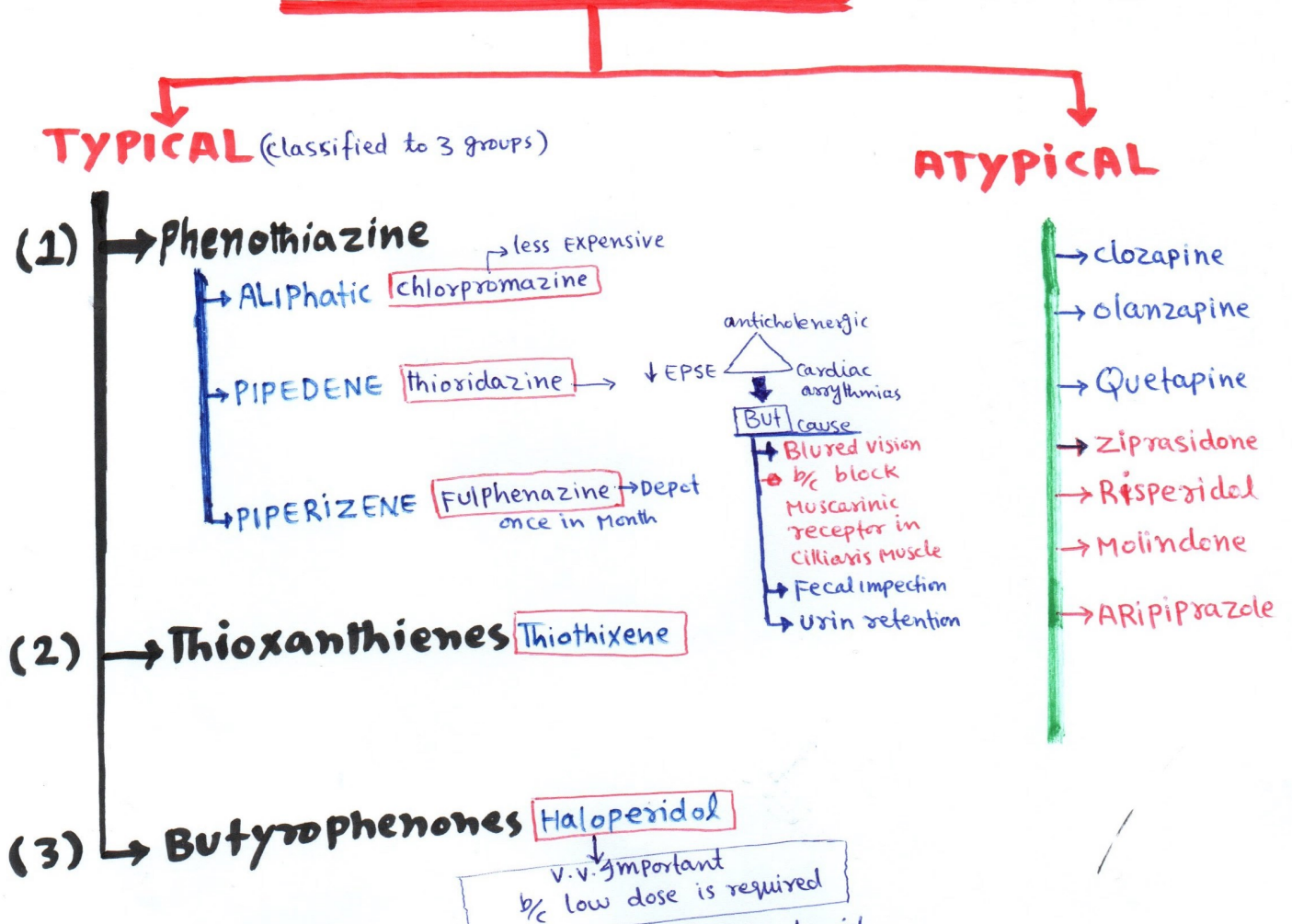
- ① ↑ed 5HT<sub>2</sub> blocker action
- ② All other actions ↓ed.
- ③ D<sub>2</sub> blocker action is not permanent, it is vibrating (i.e.: low affinity)

## ANTIPSYCHOTIC DRUGS



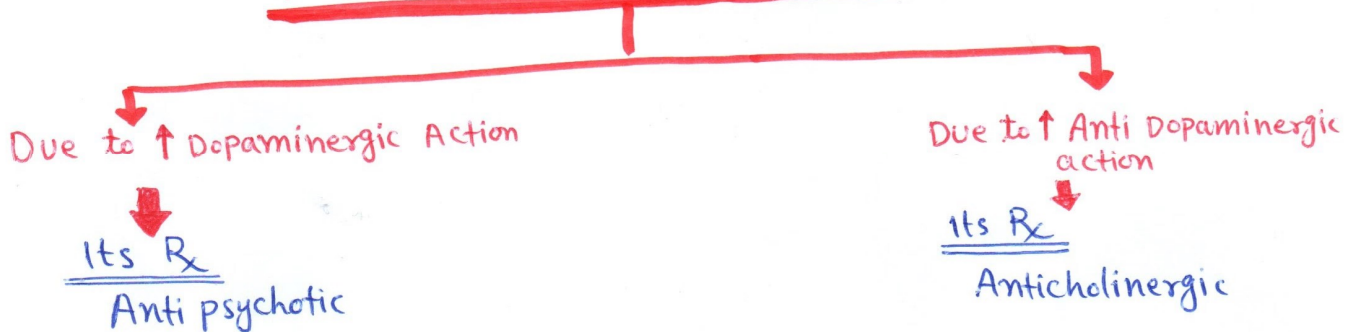


# ANTIPSYCHOTIC DRUGS classification



The E.P.S.E are very high for haloperidol b/c it block  $D_2$  receptor not only in Mesolimbic but also in nigrostriatal pathway.

## TWO TYPES OF sideeffects



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# SOME DETAIL OF ATYPICAL ANTIPSYCHOTIC DRUGS

## CLOZAPINE: it is very Toxic ☠

in 1-2% it attack on Bone marrow house, so the granulocyte count goes down, person develop severe infection.

\* In patient with clozapine in 6 months of treatment we need to check Blood Count in every week.

The remaining Atypical antipsychotic drug doesn't produce Bone marrow damage.

## OLANZAPINE

- USES
- Anti Manic
  - Anti depressant
  - Anti Anxiolytic
  - OCD (obsessive compulsive disorders)
  - Antipsychotic

## ZIPRASIDONE

produce Cardiac Arrhythmias

produce prolonge QT interval, b/c they actually prolong K<sup>+</sup> efflux during repolarization state & cause TDP (Torsa de Pontha)

TDP QRS are upward & some are downward.



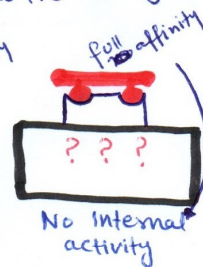
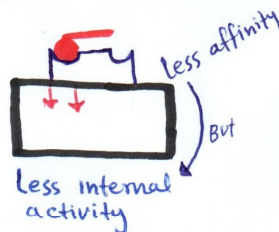
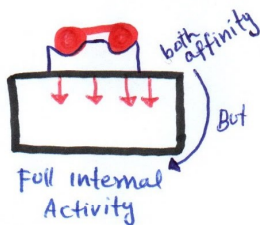
## MOLINDONE

used in Toret syndrome. (occur in children)

Toret syndrome is due to dysfunction of Caudate nucleus, so such children develop Motor ticks (Repetitive purpose of motor activity)

## ARIPIRAZOLE

it is partial agonist of D<sub>2</sub> receptor & 5HT<sub>2</sub> receptor also. It is latest Atypical antipsychotic drug.



- Funny Examples
1. your Friend come & hit you two kicks
  2. your Friend come & hit you one kick
  3. your GF come & hold you but show no reactions

AFFINITY ⇒ ability of a drug to bind with receptor  
Action ⇒ ability of a drug to stimulate receptor.



## ALLERGIC REACTIONS OF Antipsychotic

Like other drugs Antipsychotic drugs also produce allergic reactions

- ① Allergic skin reaction
- ② Allergic Hypersensitivity in Liver, Cause Jaundice
- ③ Hypersensitivity against Bone marrow (granulocytosis)
- ④ Typical antipsychotic decrease threshold for seizure, so in Epileptic patient we must be careful about treatment.

## PHARMACOKINETICS OF ANTIPSYCHOTIC DRUGS

All that drugs which acts on CNS, Must be lipid soluble, because they have to cross BBB, all those drugs which cross from BBB, also cross the placental and GIT barrier.

Drugs which are lipid soluble, they stored in E-R of hepatocytes b/c hepatocytes has more Enzymes to metabolize the drug; the metabolis of drug before entering to circulation are called "1st pass effects."

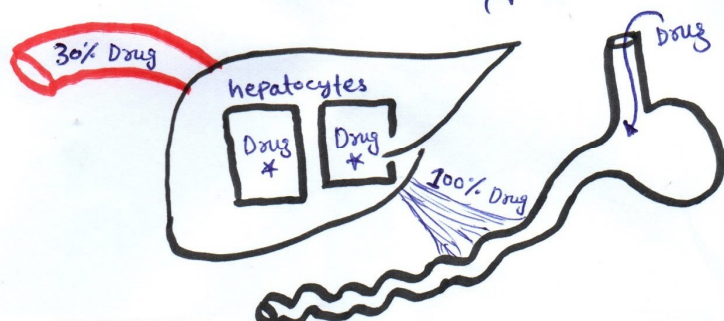
The drugs which have 1st pass effect 70% of it is metabolize in Liver before enter to circulation. & 30% of it enter to circulation.

- \* So, All Antipsychotic drug must be lipid soluble, all of them taken orally. As these drugs cross the placenta, cause Toxicity to fetus.
- \* These drugs Must be bound strongly to Plasma proteins.

To eliminate these drugs from the body, they must be converted to water soluble, so they undergo biotransformation - reduction in liver

Biotransformation reduction: which alter the drugs:

So these water soluble metabolites are then easily excreted by urine or feces.



# USES OF ANTIPSYCHOTIC DRUGS

- schizophrenia
- schizo Affective disorders
- psychosis due to
  - ↳ Drugs or
  - ↳ Toxins
- psychotic states related to
  - ↳ severe depression
  - ↳ severe Mania
- Tourette syndrome (Moudone, Pimozide) drugs
- HiccUP (chlorpromazine are used)
- Pruritis (promethazone)  
(Itching)
- Emesis (severe vomiting) → chlorpromazine are used.
- Neuroleptic Anesthesia  
↓  
Droperidole + pentalanyl  
(↓ it is an opioid drug)

\* End of Antipsychotic Drugs  
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