

Neurochemical basis of behavior & Drug therapy of schizophrenia

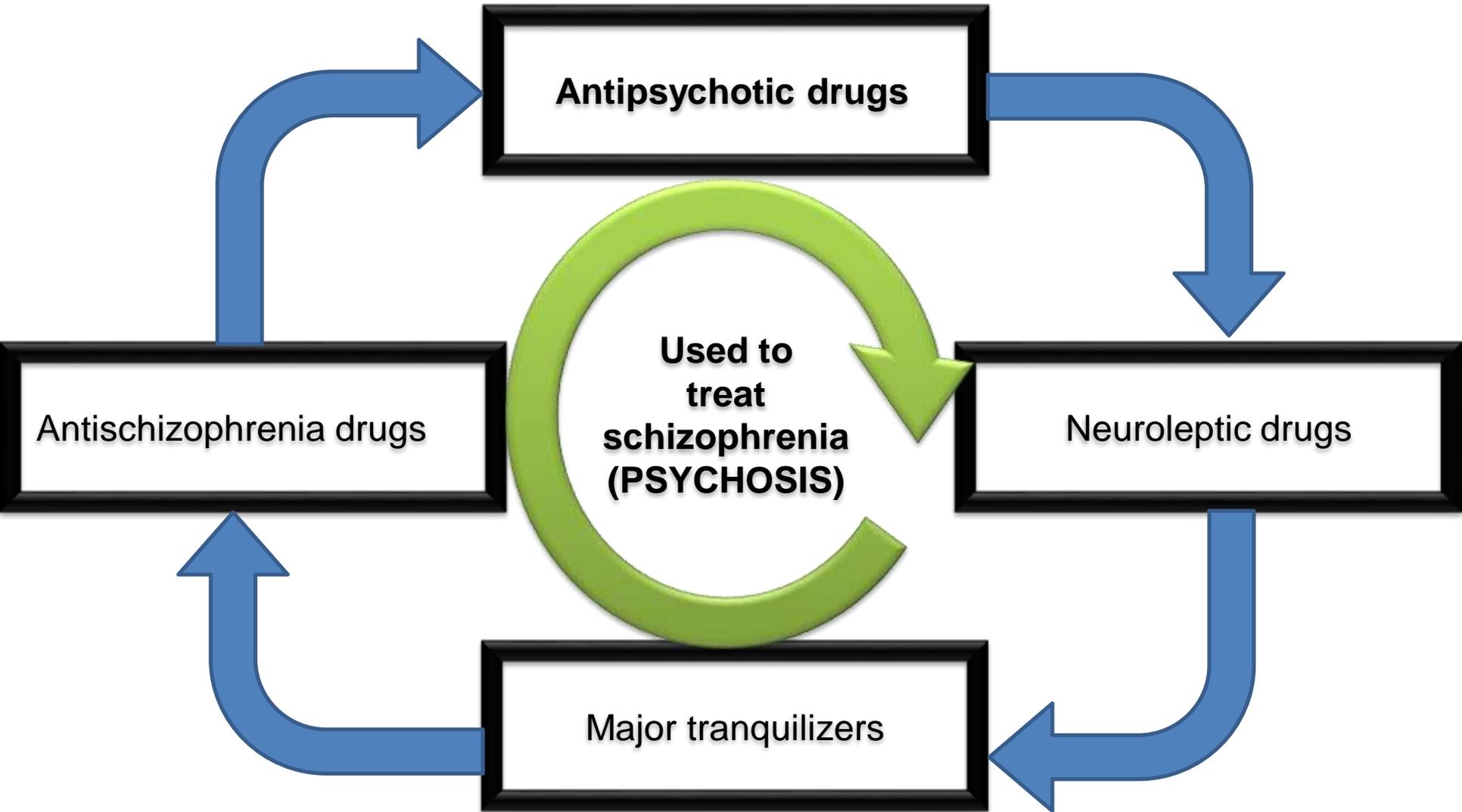


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Objectives

- 1- What is schizophrenia?
- 2- Diagnosis of schizophrenia
- 3- Etiology of schizophrenia
- 4- Pharmacological treatment of schizophrenia
- 5- Mechanism of action of antipsychotic drugs
- 6- Side effects of antipsychotic drugs



Schizophrenia

- The most debilitating mental illnesses
- Patients do not have more than one distinct personality
- 1% of the population suffer (in 12 m period)

Schizophrenia

Split

Mind

Describe the fragmented mind of people with the disorder

Is a serious brain illness which are characterized by severe problems with a person's

- thoughts,
- feelings,
- behavior,
- and use of words and language.

Clinical Picture of Schizophrenia

- Three major clusters of symptoms:
 - Positive
 - Negative
- Disorganized Functioning in work, relationships, or self-care has declined since onset
- D.D.: s [addiction](#), [bipolar disorder](#) and [depression](#)

Table 9.1 Summary of the Major Symptom Domains in Schizophrenia

Positive Symptoms	Negative Symptoms	Disorganized Symptoms
Delusions, hallucinations	Avolition, alogia, anhedonia, blunted affect, asociality	Disorganized behavior, disorganized speech

Neurochemical basis of Schizophrenia

• Dopamine Theory

– Disorder due to excess levels of dopamine

• Drugs that alleviate symptoms reduce dopamine activity

• Amphetamines, which increase dopamine levels, can induce a psychosis

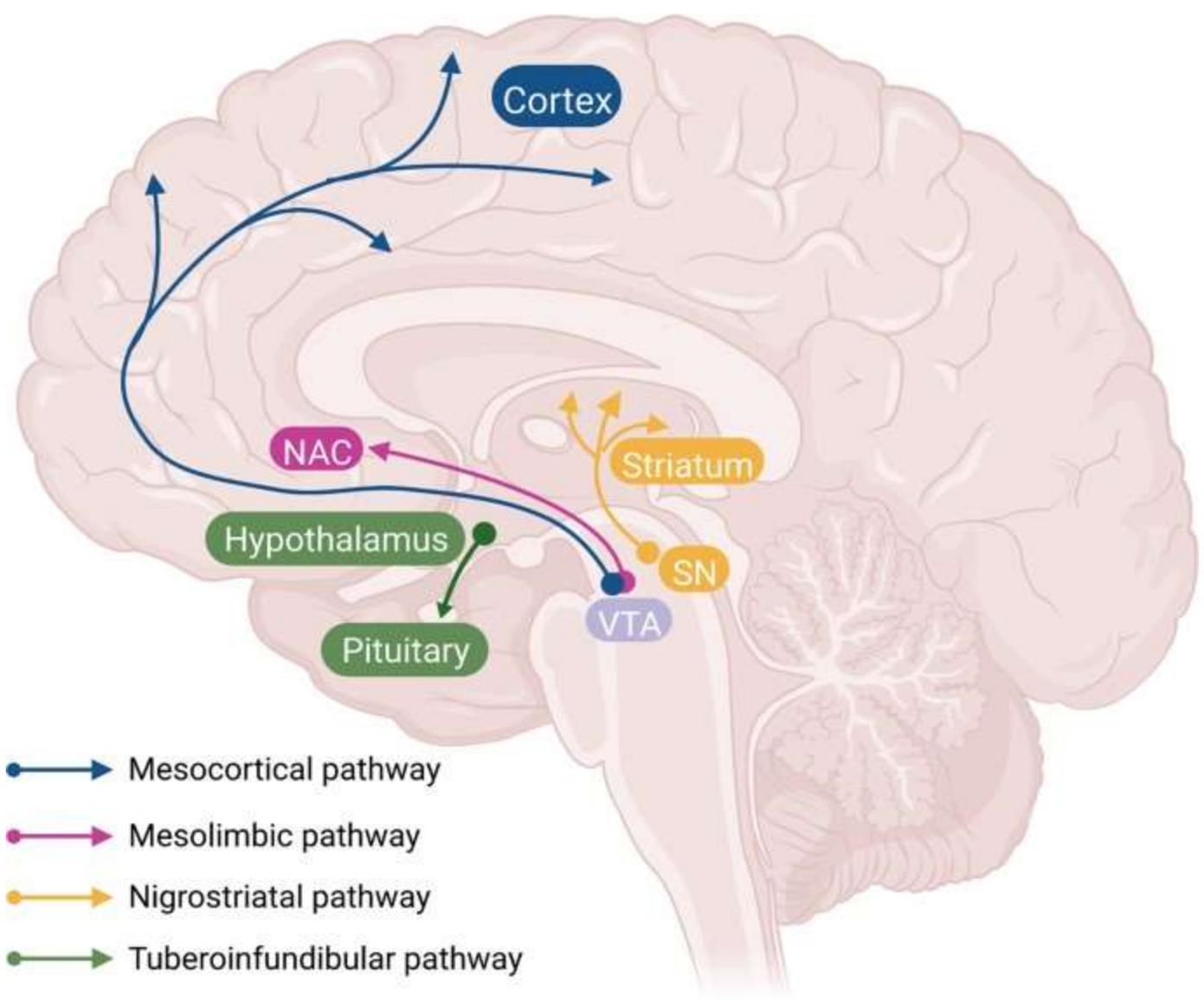
• Theory explanation:

– Excess numbers of dopamine receptors or oversensitive dopamine receptors

– Localized mainly in the mesolimbic pathway

• Mesolimbic dopamine abnormalities mainly related to positive symptoms

– Decreased dopamine activity in the mesocortical pathway mainly related to negative symptoms (increased 5HTA activity)



- → Mesocortical pathway
- → Mesolimbic pathway
- → Nigrostriatal pathway
- → Tuberoinfundibular pathway

**What do all antipsychotic
have in common?**

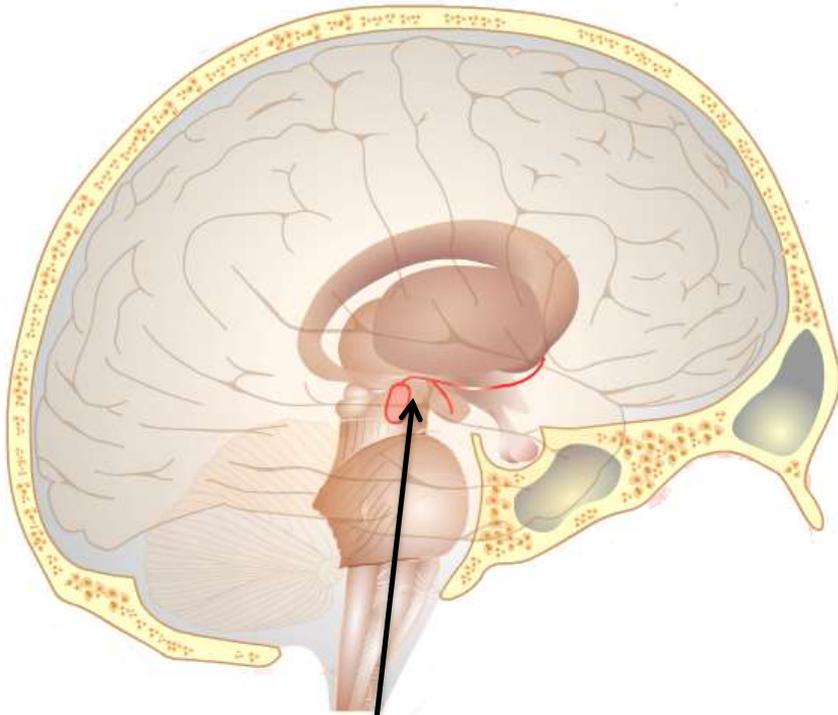
They reduce **dopaminergic** neurotransmission

Dopaminergic pathway in CNS

We will discuss only two pathways

❖ **Mesolimbic pathway**

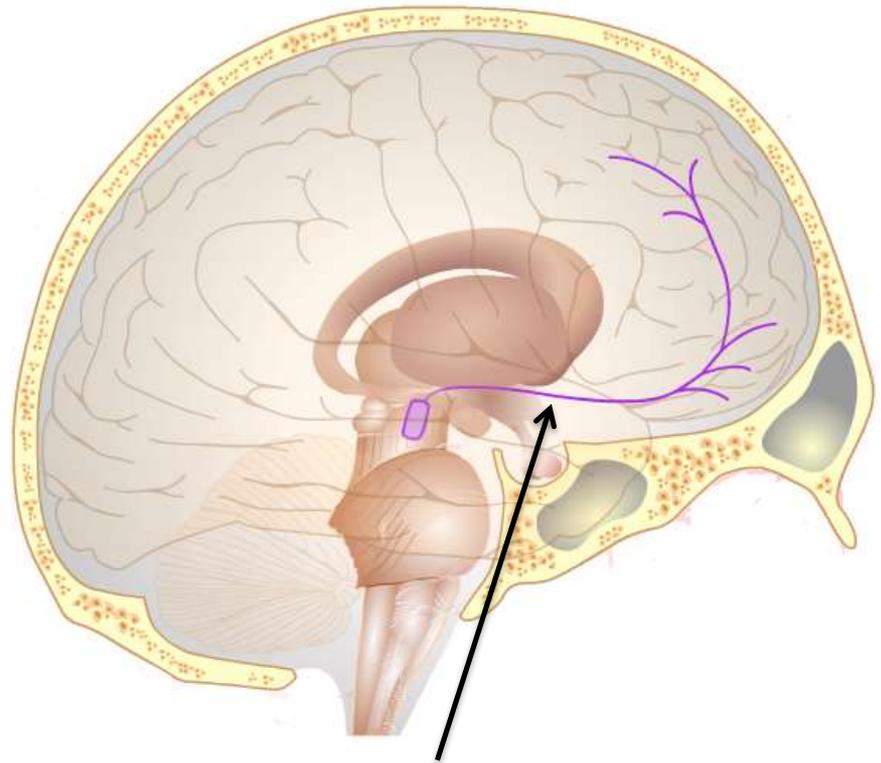
❖ **Mesocortical pathway**



Mesolimbic pathway

Excess activity implicated in:

- **Positive symptom schizophrenia**
e.g.
 - **hallucinations**
 - **delusions**



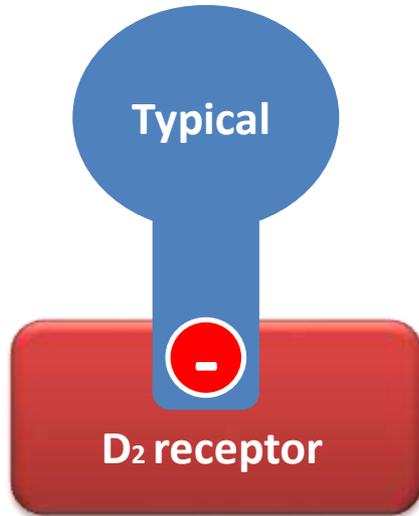
Mesocortical pathway

Diminished activity implicated in :

- **Negative symptoms of schizophrenia** e.g.
Restrictions in
 - **emotion,**
 - **thought,**
 - **speech,**
 - **pleasure and attention.**

Typical is D₂ antagonist

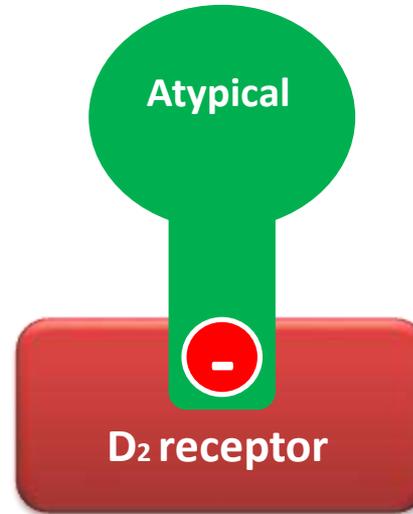
high affinity to D₂



Binding to D₂ receptor
(tight)

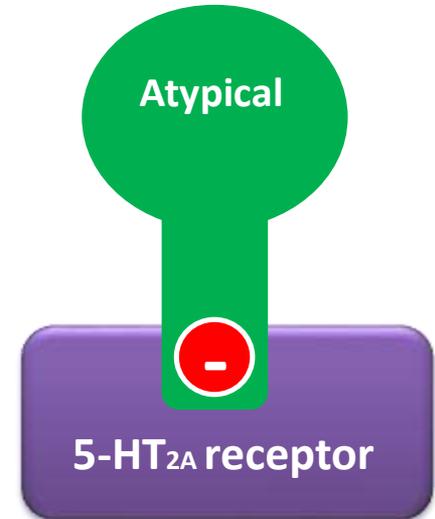
Atypical is serotonin-dopamine antagonist

Low affinity to D₂



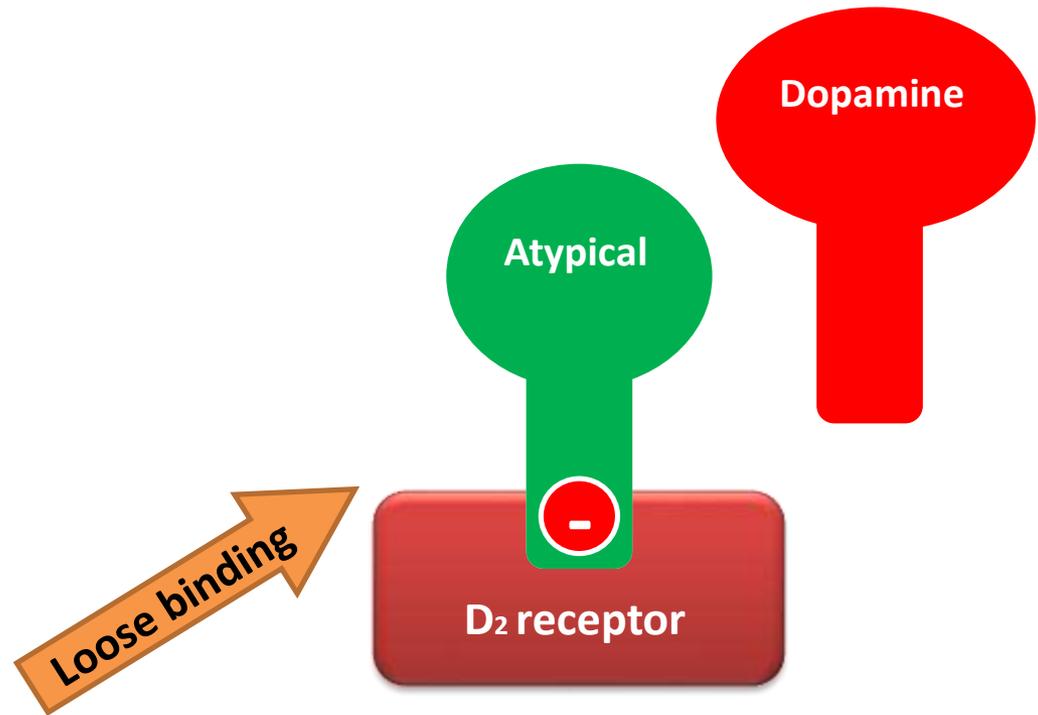
Binding to D₂ receptor
(loose)

high affinity to 5-HT_{2A}



Atypical dissociate rapidly from D₂ receptor

Atypical dissociate rapidly from D₂ receptor



High occupancy for D₂



High EPS risk

Antipsychotic efficacy

D₂ occupancy

60%

75%

78%

EPS



Which has more EPS risk typical or atypical neuroleptic? And Why?

Antipsychotic drugs

• First-generation (typical) antipsychotic medications (neuroleptics; 1950s)

–Phenothiazines (chlorpromazine)

–butyrophenones (haloperidol)

•Block dopamine receptors

•Little effect on negative symptoms

•Extrapyramidal side effects, Neuroleptic malignant syndrome

•Second-generation (atypical) antipsychotics

–Risperidone

–Olanzapine

–Clozapine

•Block serotonin receptors

•Advantages:

–Fewer motor side effects

–Less treatment noncompliance

–Reduces relapse

•Side effects

– Agranylocytosis

–Weight gain

•Newer medications may improve cognitive function:

–Olanzapine

–Risperidone

Side Effects of Antipsychotic Medications

• 1- Extrapiramidal Symptoms (EPS)

- Tremors

- **Dystonia:** Involuntary skeletal muscle contractions leading to:

- **twisting movements** in certain parts of body for a period.

- **Treatment:** Anticholinergic drugs (e.g. benztropine slow IV) or Antihistaminics (e.g. diphenhydramine)

- **Tardive dyskinesia:** repetitive involuntary movements with prolonged use

Side Effects of Antipsychotic Medications

2- Neuroleptic Malignant Syndrome (NMS): life-threatening

Due to autonomic disturbances

- Hyperthermia, muscular rigidity, tachycardia, hyper or hypotension, autonomic instability, rhabdomyolysis, confusion
- Can lead to loss of consciousness and death
- Treatment:**
- Supportive management and stop drug
- Sever cases: ICU

Side Effects of Antipsychotic Medications

3- Autonomic disturbances:

- Blocking of alpha receptors in blood vessels: postural hypotension
- Sexual dysfunctions: failure of ejaculation: non-compliance (failure of therapy)
- Atropine- like effects

Side Effects of Antipsychotic Medications

4- Endocrinal disturbances: Hyperprolactinemia

- Amenorrhea, menstrual cycle disorders, breast enlargement, galactorrhea
- Dose dependent
- Related to D2receptor affinity
- Higher in 1st generation as a class

Side Effects of Antipsychotic Medications

5- Polyphagia: Weight Gain and Metabolic Syndrome:

- due to blocking of 5HT_{2A} receptors in satiety center.
- More with atypical drugs

Side Effects of Antipsychotic Medications

6- Haematological

- Mild leukopenia common to all
- Agranulocytosis and neutropenia infrequent:
may be fatal
 - If occurs, stop drug
- Highest risk in clozapine
 - Especially at beginning

Side Effects of Antipsychotic Medications

- **7- CVS:**

- **Aarrhythmias, and orthostatic hypotension)**

- **Antipsychotic drugs with increased risk included haloperidol, olanzapine, risperidone**

- **8- Cholestatic jaundice: cholorpromazine**

Summary

	Typical drugs	Atypical drugs
Members	Chlorpromazine, haloperidol	Risperidone, olanzapine, clozapine
Mechanism of action	Block D2 receptors	Block 5HT2A receptors
Efficacy	Positive symptoms	Negative symptoms
Extrapyramidal symptoms	+++	+
Neuroleptic malignant syndrome	+++	+
Polyphagia	-	+++
Agranulocytosis	+	+++



- **Thank you**