Neurochemical basis of behavior
&
Drug therapy of schizophrenia

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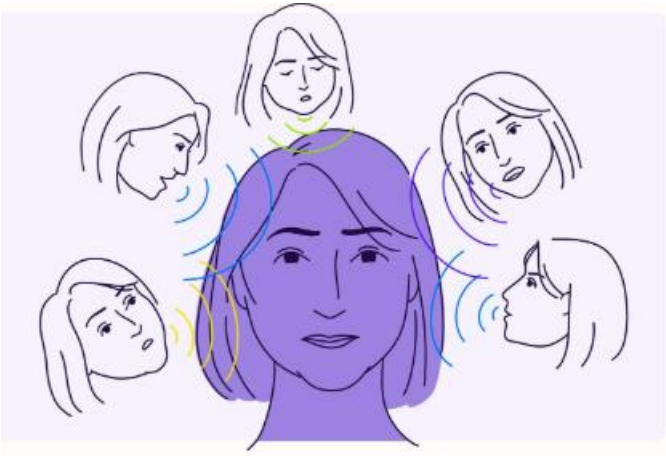
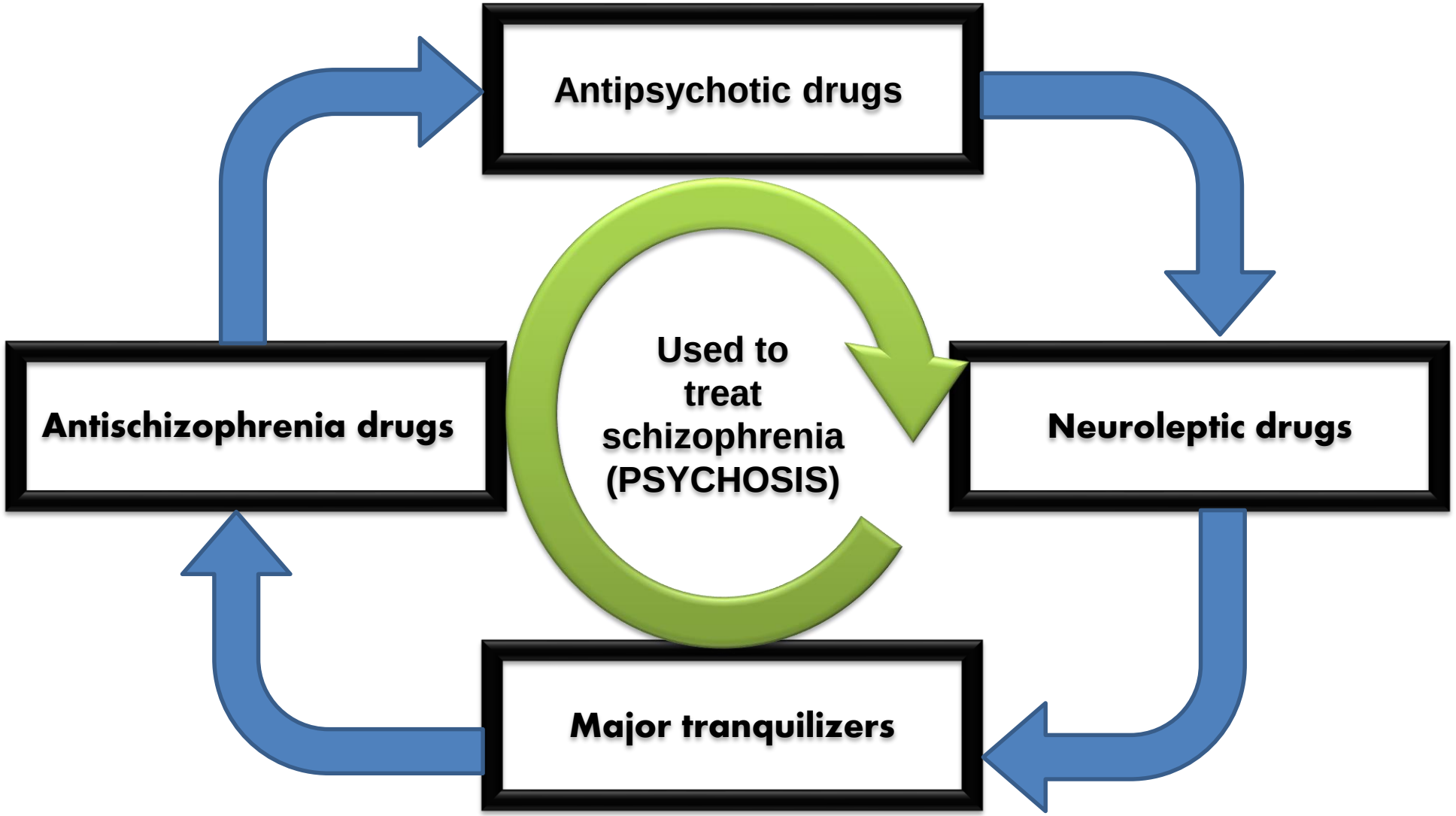


Objectives

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


Antipsychotic drugs
Neuroleptic drugs
Major tranquilizers
Antischizophrenia drugs
Used to treat schizophrenia (PSYCHOSIS)

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.**

Diagnosis of Schizophrenia

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

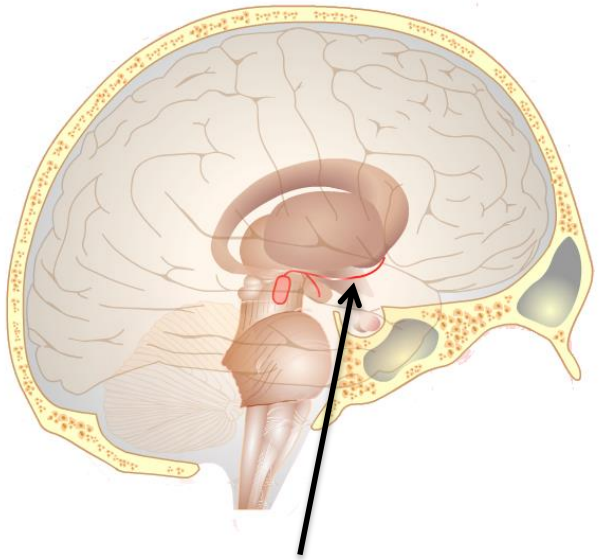
Table 9.1 Summary of the Major Symptom Domains in Schizophrenia

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

Neurochemical basis of Schizophrenia

- **Dopamine Theory**
- **Schizophrenia is due to**: **excess levels of dopamine**
- **Evidence**: 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**)

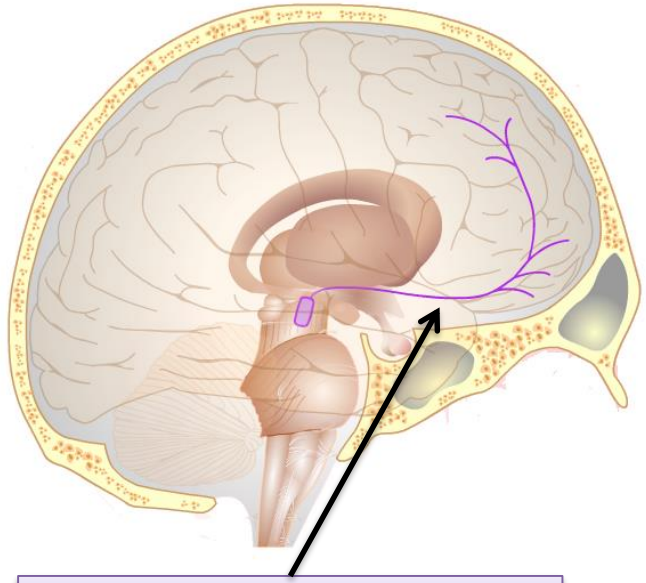
Dopaminergic pathway in CNS



Mesolimbic pathway

Excess activity implicated in:

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



Mesocortical pathway

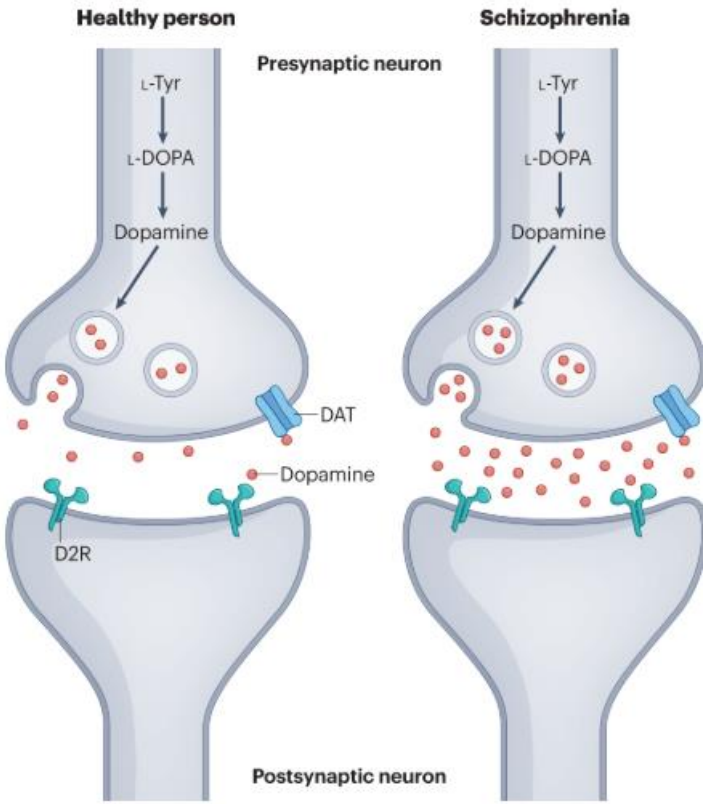
Diminished activity implicated in :

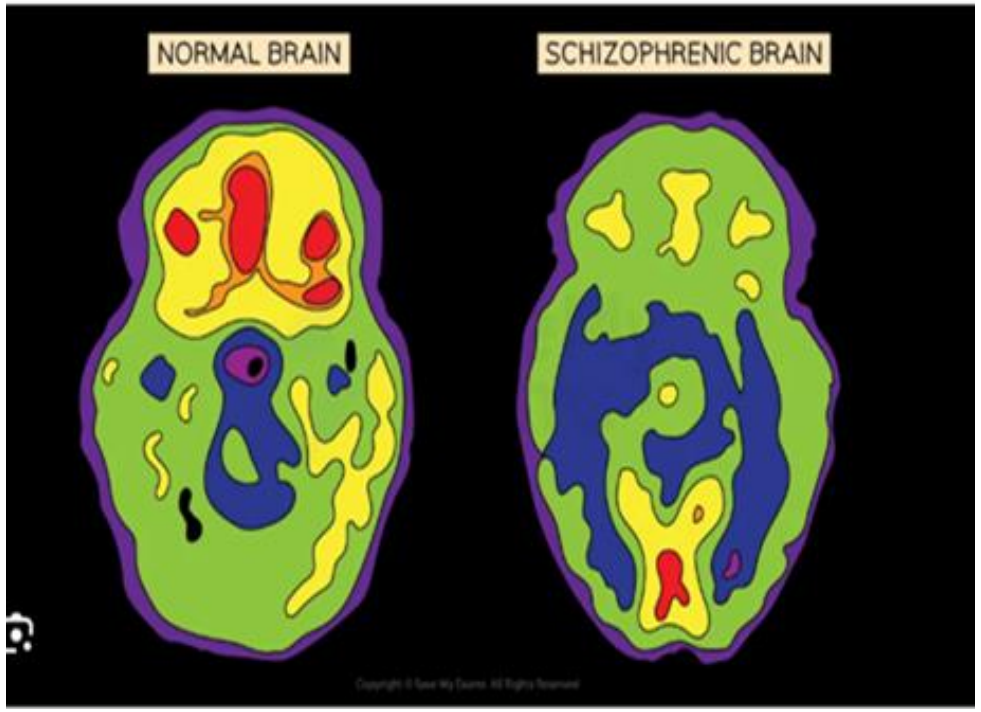
- **Negative symptoms of schizophrenia e.g.**

Restrictions in

- **emotion,**
- **thought,**
- **speech,**
- **pleasure and attention.**

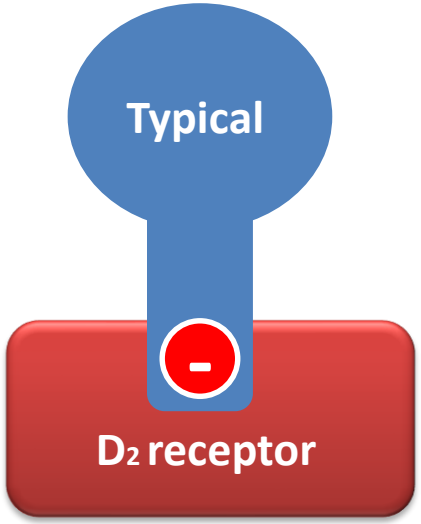
Dopamine theory of schizophrenia





Typical is D_2 antagonist

high affinity to D_2

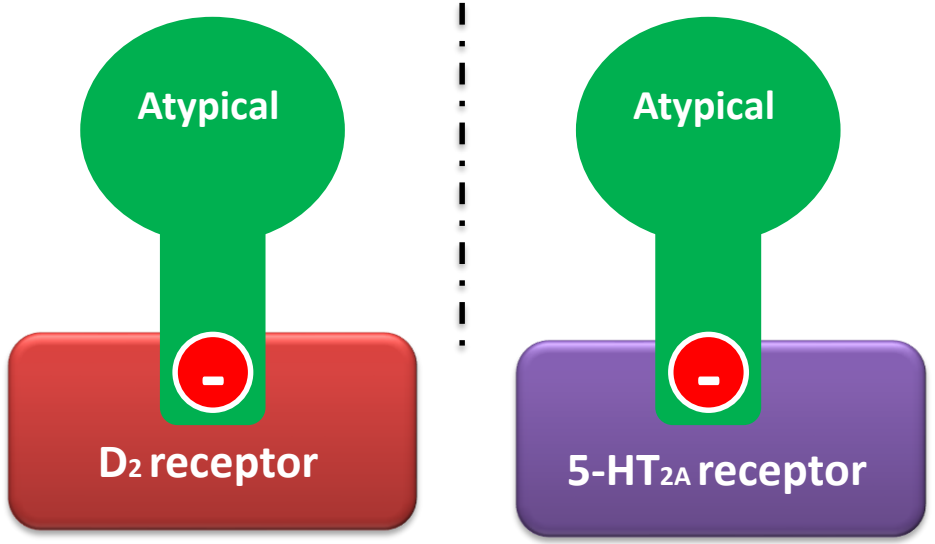


Binding to D_2 receptor
(tight)

Atypical is serotonin-dopamine antagonist

Low affinity to D_2

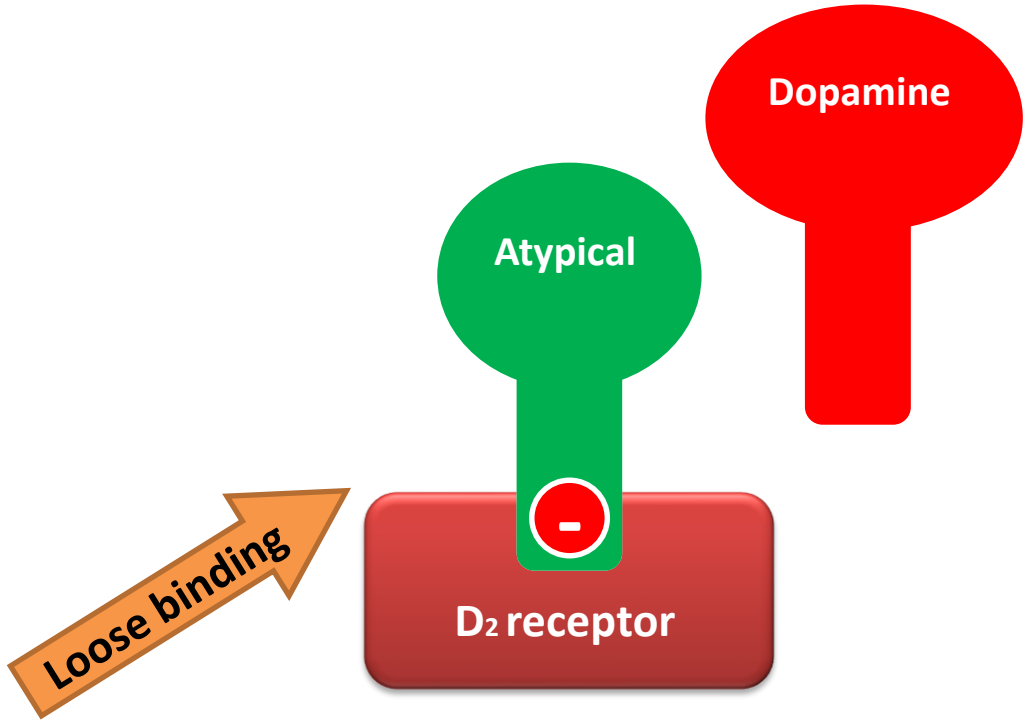
high affinity to 5-HT_{2A}



Binding to D_2 receptor
(loose)

Atypical dissociate rapidly from D_2 receptor

Atypical dissociate rapidly from **D_2 receptor**



High occupancy for D_2 → High EPS risk

Antipsychotic efficacy

D_2 occupancy

60%

75%

78%

EPS

Antipsychotic drugs

- **First-generation (typical) antipsychotic medications (neuroleptics)**
  - ❑ **Phenothiazines** (**chlorpromazine**)
  - ❑ **Butyrophenones** (**haloperidol**)
- **Mechanism of action**: Block dopamine receptors: **relieve positive symptoms**
- **Disadvantages**:
- 1- Little effect on negative symptoms
- 2- Extrapyramidal side effects, Neuroleptic malignant syndrome

Second-generation (atypical) antipsychotics

- **Risperidone , Olanzapine, Clozapine, Quetiapine**

•**Mechanism of action: Block serotonin** receptors and **dopamine receptors** (loose binding: **low risk of both EPS and hyperprolactinemia**)

•**Advantages:**

1- Fewer motor side effects (extrapyramidal)

2- Less noncompliance

3- Reduce relapse

•**Side effects**

1- Agranulocytosis

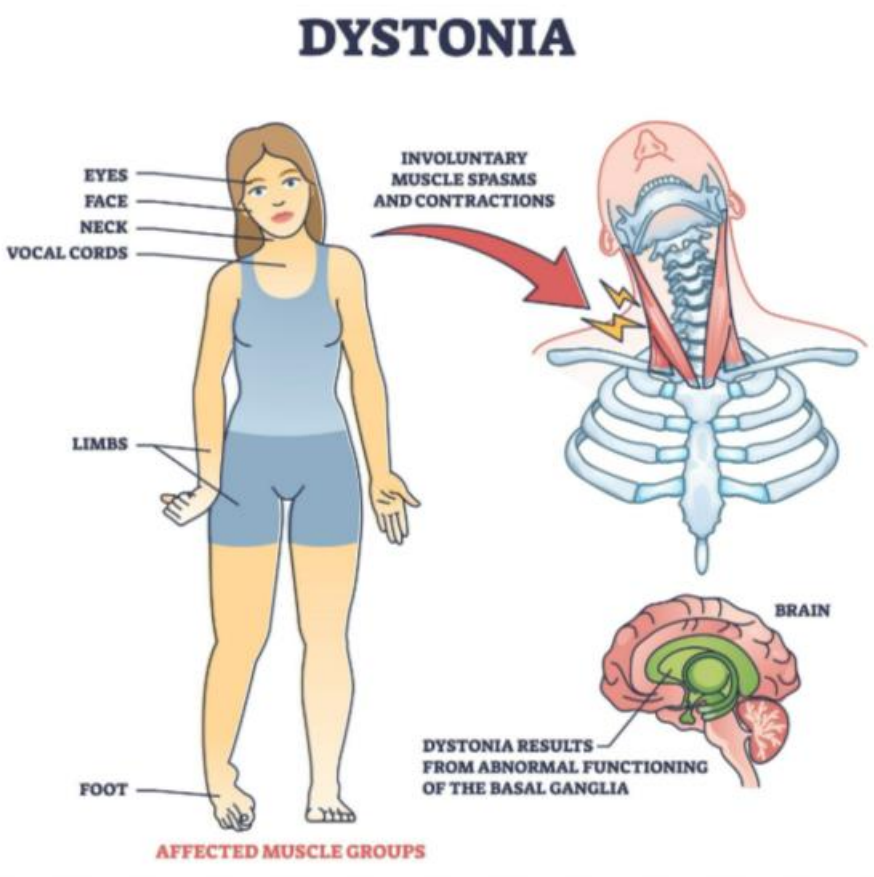
2- Weight gain

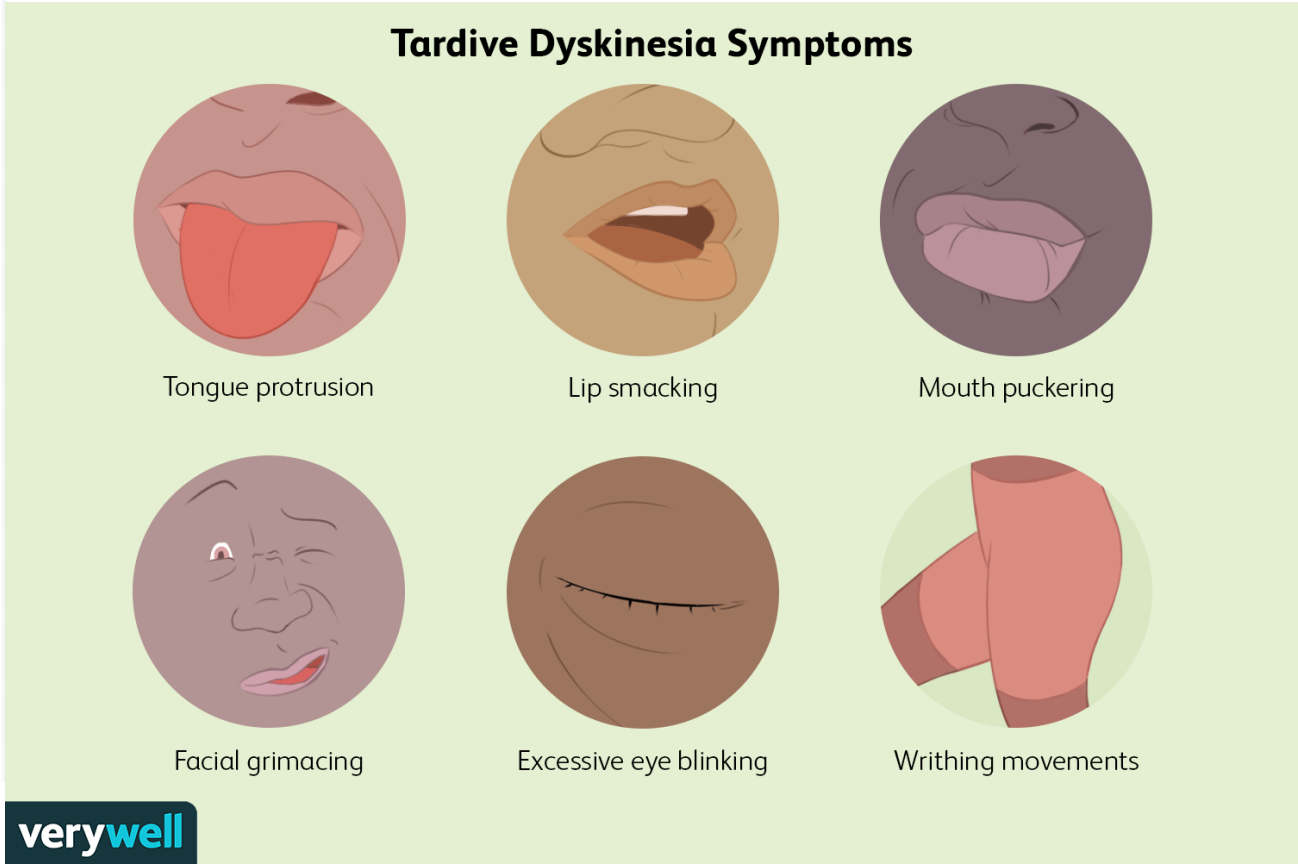
•**Newer medications may improve cognitive function:**

- Olanzapine
- Risperidone

Side Effects of Antipsychotic drugs

- **1- Extrapyramidal 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


DYSTONIA
EYES
FACE
NECK
VOCAL CORDS
LIMBS
FOOT
INVOLUNTARY MUSCLE SPASMS AND CONTRACTIONS
BRAIN
DYSTONIA RESULTS FROM ABNORMAL FUNCTIONING OF THE BASAL GANGLIA
AFFECTED MUSCLE GROUPS


Tardive Dyskinesia Symptoms
Tongue protrusion
Lip smacking
Mouth puckering
Facial grimacing
Excessive eye blinking
Writhing movements
verywell

Side Effects of Antipsychotic Medications

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

Due to autonomic disturbances

•Hyperthermia, muscular rigidity, tachycardia, hyper or hypotension,, rhabdomyolysis, confusion

•**Complications**: Coma and death

•**Treatment:**

•Stop drug

•Supportive management and

•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 5HT2A receptors in satiety center.
- More with atypical drugs

Side Effects of Antipsychotic Medications

6- Hematological

- **Mild leukopenia:** common
- **Agranulocytosis** and **neutropenia** infrequent: may be **fatal**
- **Management:** stop the drug
- **Highest risk** in clozapine, at beginning of treatment

Side Effects of Antipsychotic Medications

- **7- CVS:**
- **Arrhythmias**
- **Orthostatic hypotension)**
- **Antipsychotic drugs with increased risk:**
- **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, hyperprolactinemia	+++	+
Neuroleptic malignant syndrome	+++	+
Polyphagia	-	+++
Agranulocytosis	+	+++

References

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- **Thank you**