



Neurochemical basis of behavior & Drug therapy of schizophrenia

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JORDAN 2025/2026 •



Objectives

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

What is schizophrenia?

- **Schizophrenia** is a chronic (long-term) mental health condition that affects interpretation of reality.
- It is a type of mental health disorder known as **psychosis** **الذهان**, which means **inability to understand what is real and what isn't**.
- Schizophrenia symptoms can significantly impact many areas of a person's life, including relationships, work, education, and physical health.

Etiology of schizophrenia

- It isn't fully understood what causes schizophrenia, but it is believed to be a **combination of genetic and environmental factors**.
- **Risk factors:**
- A family history of schizophrenia
- CNS infection or autoimmune disease
- Extreme stress over a long period of time
- Lead exposure
- Living in a densely populated environment
- Disorders during pregnancy, such as [gestational diabetes](#), [pre-eclampsia](#), [malnutrition](#), or [vitamin D deficiency](#)
- Low birth weight
- Birth complications
- Recreational drug use, particularly amphetamine and marijuana use at an early age

Diagnosis of schizophrenia

- Symptoms of schizophrenia may vary from person to person, but often include problems with cognition (thinking), perception and affect (emotions).
- Symptoms may also change, improve, or worsen over time.
- In males , symptoms commonly start in the early to mid-twenties and in females in the late twenties.
- Patients with schizophrenia do NOT have a “split personality” and the condition does NOT usually cause people to become violent.

Symptoms of schizophrenia

- **Two major clusters of symptoms:**
 - **Positive**
 - **Negative**
- D.D. (differential diagnosis):
- addiction, bipolar disorder and depression

Positive Symptoms of Schizophrenia

1. Hallucinations
2. Delusions
3. Disorganized thinking
4. Abnormal motor behaviors



Negative symptoms of schizophrenia

NEGATIVE SYMPTOMS

BLUNTED EFFECT

ALOGIA

AVOLITION

ASOCIALITY

ANHEDONIA

CONSTRUCTS

DIMINISHED EXPRESSION

AVOLITION/
APATHY

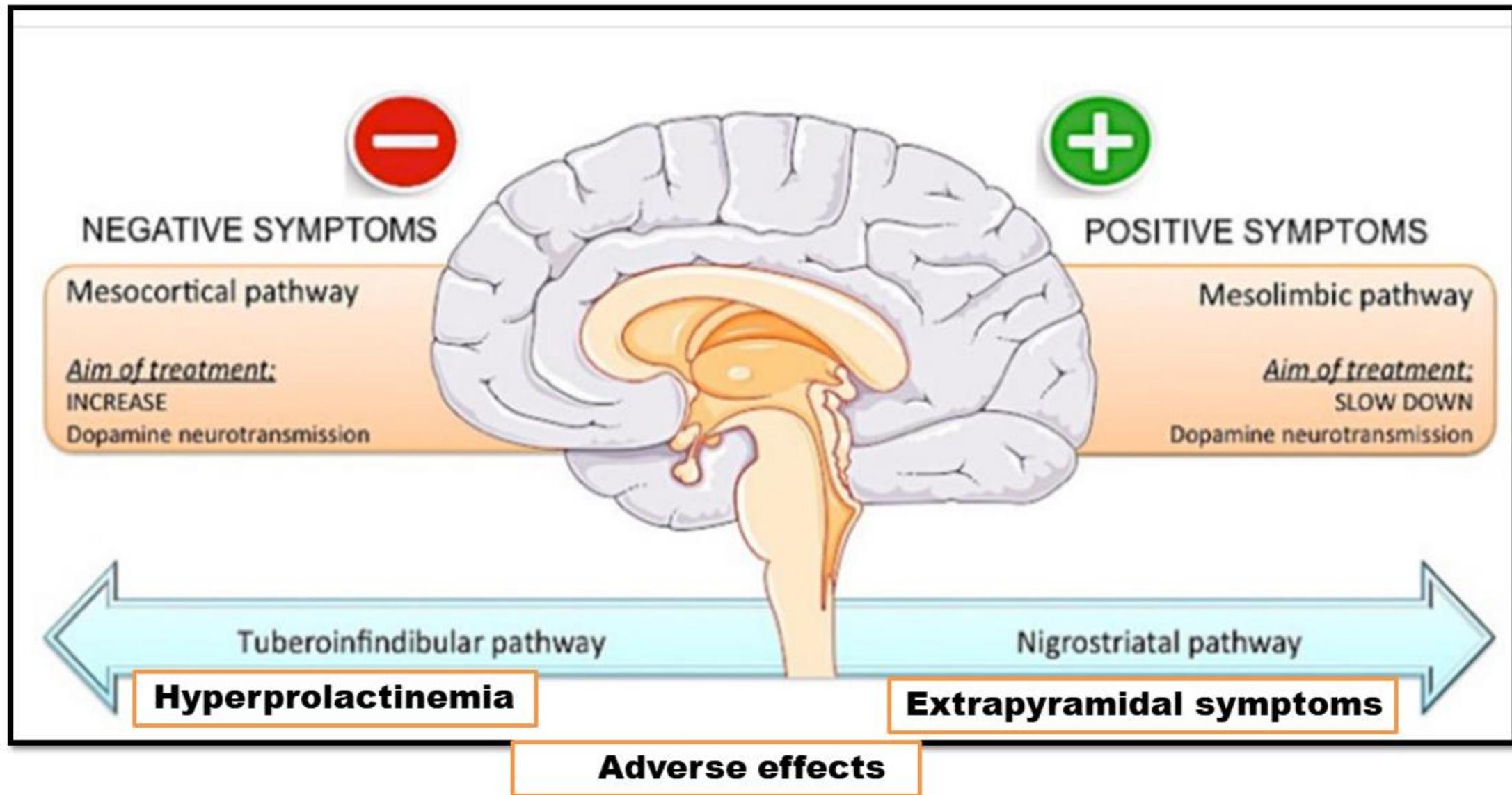


1. Blunted affect: Decreased expression of emotion
2. Alogia: Reduction in quantity of words spoken
3. Avolition: Reduced initiation and persistence of goal-directed activity due to decreased motivation
4. Asociality: Reduced social interactions and initiative due to decreased interest in relationships with others
5. Anhedonia: Reduced experience of pleasure during an activity or in anticipation of an activity. (Consummatory / Motivational Anhedonia)

Neurochemical basis of Schizophrenia

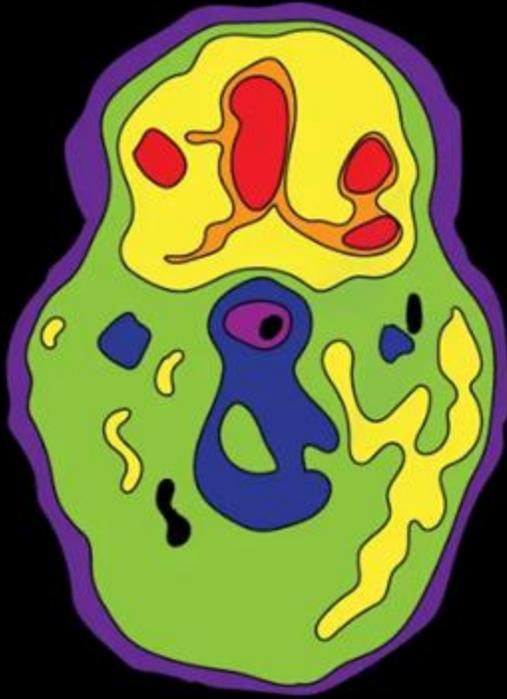
- **Dopamine theory:**
- Psychosis in schizophrenia originates from *excessive dopamine activity (hyperactivity)* in the mesolimbic pathway, causing positive symptoms like hallucinations
- While *low dopamine (hypoactivity)* in the prefrontal cortex (mesocortical pathway) leads to negative symptoms (increased 5HTA activity).
- **Evidence & Support**
- **1- Antipsychotic Drugs:** Block dopamine D2 receptors, reducing positive symptoms.
- **2- Dopamine Agonists:** Drugs like amphetamines can induce psychosis, mimicking schizophrenia.
- **3- Brain Imaging:** Shows increased dopamine receptor density in some brain areas of patients with schizophrenia.

Dopamine theory of schizophrenia



Evidence of dopamine theory

NORMAL BRAIN



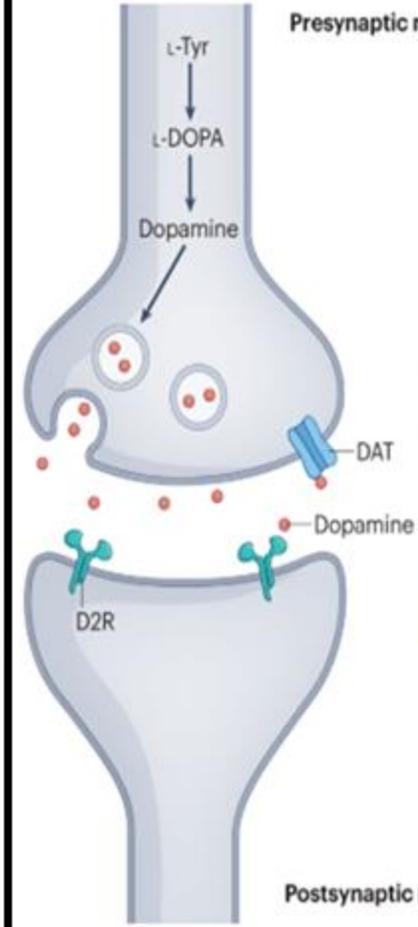
SCHIZOPHRENIC BRAIN



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These PET scans show much lower activity in the frontal lobes of the schizophrenic brain which could be evidence of hypodopaminergia.

Healthy person



Schizophrenia

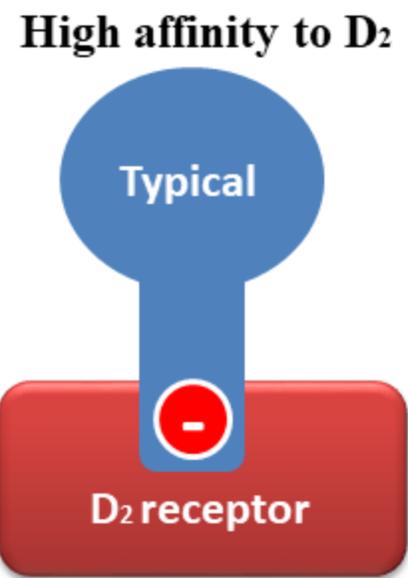


Postsynaptic neuron

Classification of antipsychotic drugs (neuroleptics)

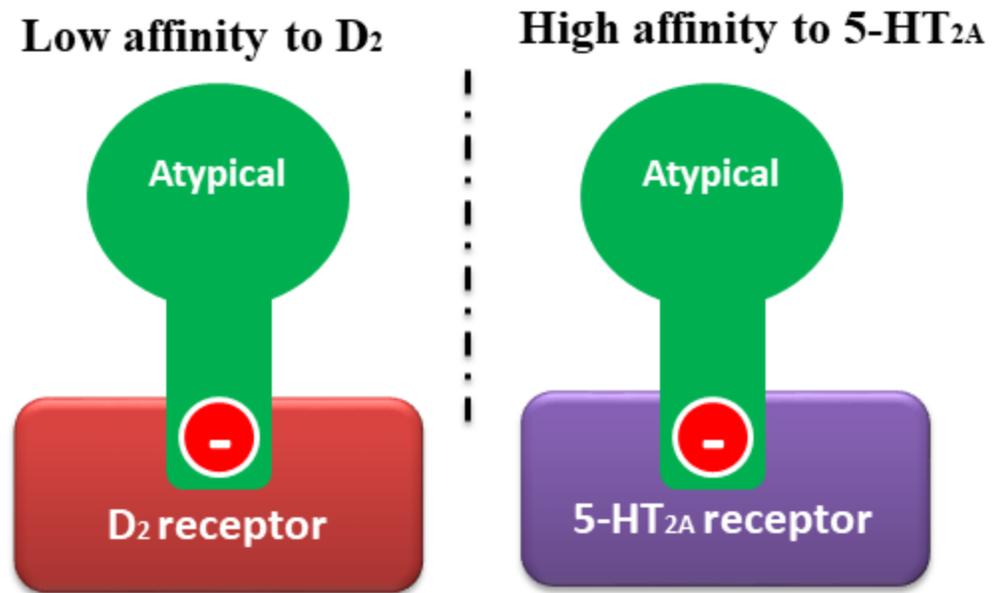
Drugs	Mechanism of action	Advantages	Disadvantages	Examples
First generation: Typical (older drugs)	<ul style="list-style-type: none"> Block <u>D2 dopamine receptors</u>: <u>high affinity</u> (<u>tight binding</u>) 	<ul style="list-style-type: none"> Effectively treating positive symptoms 	<ul style="list-style-type: none"> Movement disorders (extrapyramidal symptoms). Negative symptoms NOT affected Neuroleptic malignant syndrome 	<ul style="list-style-type: none"> Haloperidol Chlorpromazine Fluphenazine.
2nd generation: Atypical (newer drugs)	<ul style="list-style-type: none"> Block <u>dopamine D2 and serotonin receptors (5HT2A)</u>: <u>less affinity to dopamine receptors</u> (<u>loose binding</u>) 	<ul style="list-style-type: none"> Better for negative symptoms Extrapyramidal symptoms : less risk Less risk of hyperprolactinemia Less non-compliance Reduce relapse 	<ul style="list-style-type: none"> Metabolic side effect Positive symptoms less affected 	<ul style="list-style-type: none"> Risperidone Olanzapine Quetiapine Clozapine
Dopamine partial agonists (DAPAs)	<ul style="list-style-type: none"> <u>Dopamine partial agonist</u>: increasing it when low and decreasing it when it is high <u>High affinity D3 receptors</u> and <u>serotonin:5-HT1A receptors</u>. 	<ul style="list-style-type: none"> Both positive and negative symptoms are affected 	<ul style="list-style-type: none"> Akathisia Sedation 	<ul style="list-style-type: none"> Aripiprazole Cariprazine

Typical is D₂ antagonist



Binding to D₂ receptor
(tight)

Atypical is serotonin-dopamine antagonist



Binding to D₂ receptor
(loose)

Atypical dissociate rapidly from D₂ receptor

High D₂Occupancy, High EPS Risk

Antipsychotic efficacy

D₂occupancy

60%

75%

78%

EPS



Adverse effects of Antipsychotic drugs

• 1- Extrapyramidal Symptoms (EPS)

• Tremors

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

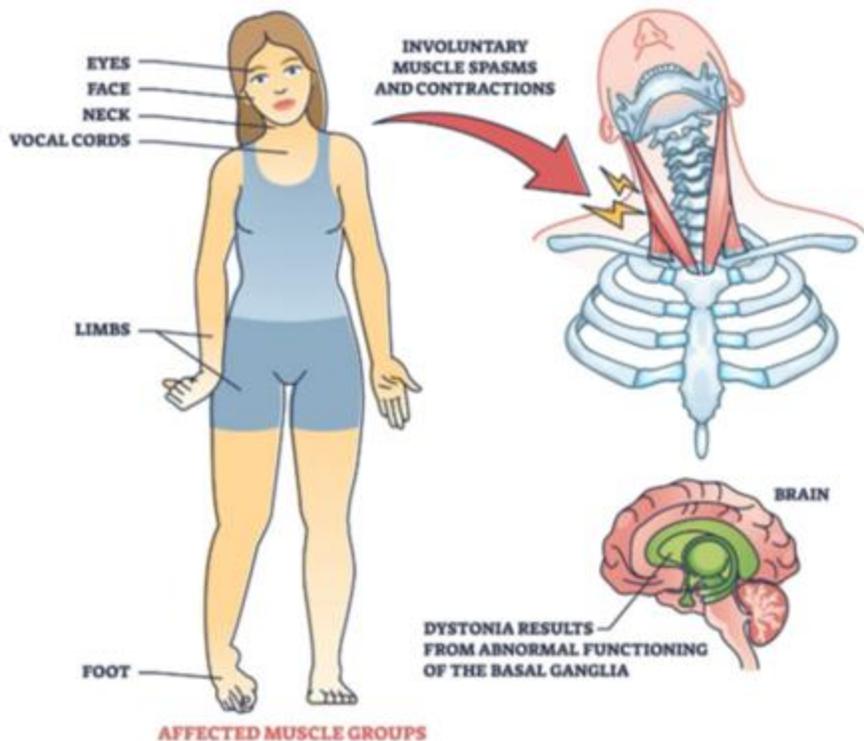
• **twisting movements** in certain parts of body for a period.

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

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

Extrapyramidal symptoms

DYSTONIA



Tardive Dyskinesia Symptoms



Tongue protrusion



Lip smacking



Mouth puckering



Facial grimacing



Excessive eye blinking



Writhing movements

ADRs of Antipsychotic drugs

- **2- Akathisia:**
- **Internal restlessness:** A deep, uncomfortable feeling of needing to move.
- **Fidgeting:** Shifting weight, swinging legs, pacing, or rocking.
- **Compulsion to move:** Inability to sit or stand still.
- **Emotional distress:** Anxiety, irritability, dysphoria, and sometimes aggression or suicidal ideation
- **Common with:** first generation drugs and DAPAs
- **Management:** dose reduction, switching drugs and benztropine



Akathisia

ADRs of Antipsychotic Medications

3- 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

ADRs of Antipsychotic Medications

4- Autonomic disturbances:

- **Blocking of alpha** receptors in blood vessels: **postural hypotension**
- **Sexual dysfunctions:** failure of ejaculation: non-compliance (failure of therapy)
- **Atropine- like effects**
- **More prominent with first generation**

ADRs of Antipsychotic Medications

5- Endocrinal disturbances: Hyperprolactinemia

Amenorrhea, menstrual cycle disorders, breast enlargement, galactorrhea

- **Dose-dependent**
- **Related to D2-receptor affinity (tuberoinfundebular pathway)**
- **Higher in 1st generation drugs**

ADRs of Antipsychotic Medications

6- Polyphagia:

- Weight Gain and Metabolic Syndrome:
- Due to blocking of 5HT_{2A} receptors in satiety center.
- More with atypical drugs

ADRs of Antipsychotic Medications

7- Hematological

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

ADRs of Antipsychotic Medications

• 8- CVS:

- **Arrhythmias**

- **Orthostatic hypotension)**

- **Antipsychotic drugs with increased risk:**

- **Haloperidol, olanzapine, risperidone**

• 9- Cholestatic jaundice:

- chlorpromazine

ADRs of Antipsychotic Medications

- **10- Cognitive dysfunction: (brain fog):**
- Decline in thinking skills like memory, focus, and problem-solving, affecting daily function and quality of life
- **Common with: first generation drugs, olanzapine and risperidone**

To summarize....

	Typical drugs	Atypical drugs	DAPAs
Mechanism of action	Block D2 receptors: high affinity, tight binding	Block 5HT2A receptors, D2: less affinity and loose binding	Block D3, 5HT1A: high affinity
Efficacy	Positive symptoms	Negative symptoms	Both positive & negative
Extrapyramidal symptoms, hyperprolactinemia	+++	+	+
Neuroleptic malignant syndrome	+++	+	+
Polyphagia	-	+++	-
Agranulocytosis	+	+++	-
Akathisia	+++	+	+++
Cognitive impairment	+++	++	-

References

Lippincott's Illustrated Review

Pharmacology, 8th edition

Lippincott Williams & Wilkins

Katzung by Anthony Trevor, Bertram Katzung, and Susan Masters . 16th
edition McGraw Hill,

Rang & Dale's Pharmacology: by Humphrey P. Rang ; James M.
Ritter ; Rod Flower Churchill Livingstone; 10th edition

Thank you