



# Neurochemical basis of behavior & Drug therapy of schizophrenia

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# 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

Psychosis

فروع من

# What is schizophrenia? الفصام

- **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

Cognition: الإدراكية  
Perception: الحسية  
Affect: الوجدان

- 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. ①
- Patients with schizophrenia do NOT have a “split personality” and the condition does NOT usually cause people to become violent. ②

# Symptoms of schizophrenia

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

# Positive Symptoms of Schizophrenia

+ve

كل الحواس يمكن تحه فيهم بدون مؤثر اكثر فيه (بسمع شلالات مت موجوده) - حقيته

1. Hallucinations Perception without Presence of Stimulus
2. Delusions Cognition : False believe inspite of Evidence. *خللات*
3. Disorganized thinking
4. Abnormal motor behaviors

عكس شعورك  
وثقافتك ودقك  
أسهرت :-  
الأمنيه  
(حد ابراقه)

1. Stalker
2. جنون العظمة
3. الفيرة
4. Somatic (عند مرضي البده... الخ)
5. Mixed

حوادث غير طبيعيه :- ضحك بالفزار

Catatonic -  
staring in )  
blank for  
(hours



Inability to do.

# Negative symptoms of schizophrenia

**NEGATIVE SYMPTOMS**

**BLUNTED EFFECT**

و جهان مسطح : تعابير وجهية  
سواء فرح، حزنا ...

**ALOGIA**

يوقف كلام  
او يقلل .

**AVOLITION**

انقمام الإرادة

**ASOCIALITY**

عزلة اجتماعية .

**ANHEDONIA**

inability to feel  
pleasurf .  
عدم القدرة على المتكور  
بالسعادة

**DIMINISHED  
EXPRESSION**

**AVOLITION/  
APATHY**



**CONSTRUCTS**

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

الدوبامين يزيد في أماكن ويقبل في أماكن.

- **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)**.   
 [↓ Dopamin, ↑ Serotonin] in mesocortical ⇒ -ve
- **Evidence & Support** إثبات نظرية
- **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

العلاج: نزود الدوبامين  
ونقل السيروتونين

العلاج + نقل الدوبامين هو



NEGATIVE SYMPTOMS

POSITIVE SYMPTOMS

Mesocortical pathway

Mesolimbic pathway

*Aim of treatment:*

INCREASE

Dopamine neurotransmission

*Aim of treatment:*

SLOW DOWN

Dopamine neurotransmission

تكتلين مهورات  
- hyperprolactinemia

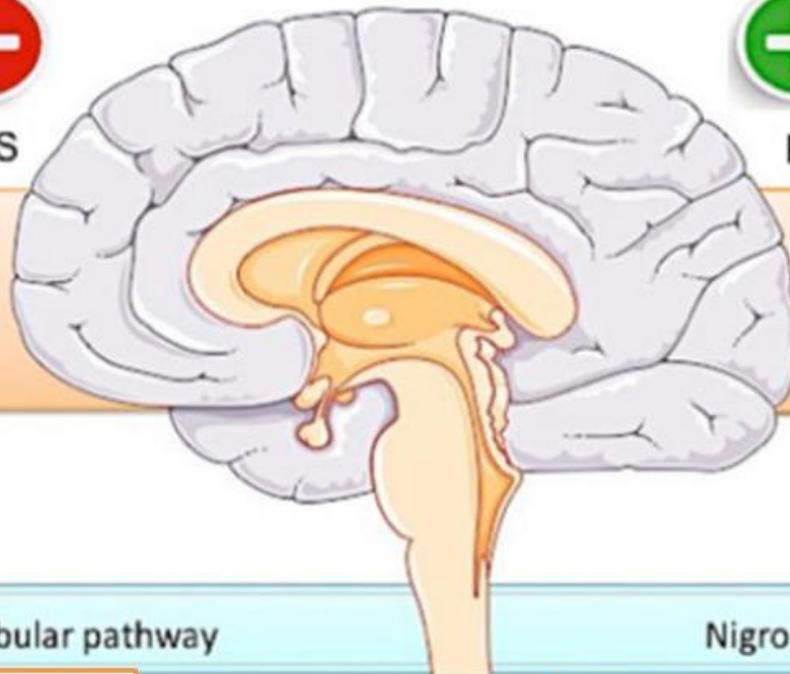
Tuberoinfundibular pathway

Nigrostriatal pathway

**Hyperprolactinemia**

**Extrapyramidal symptoms**

**Adverse effects**



الدوبامين : Dopamine

## Evidence of dopamine theory

NORMAL BRAIN

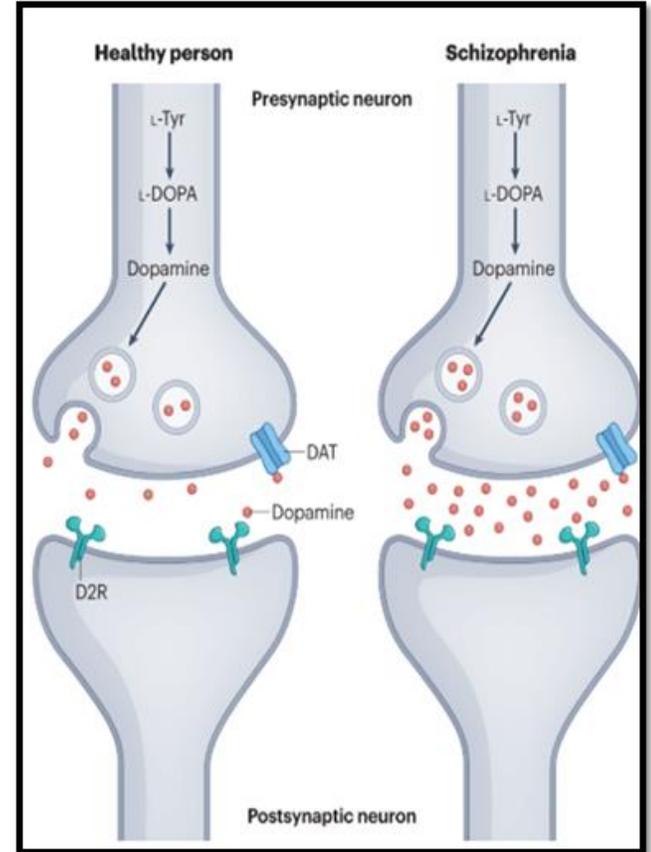


SCHIZOPHRENIC BRAIN



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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.

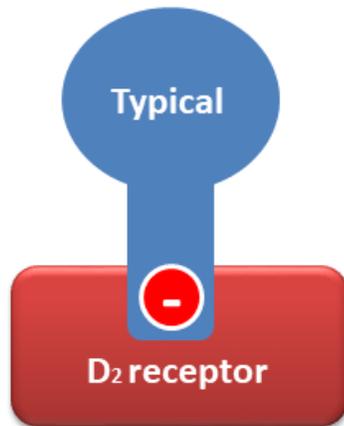


# Classification of antipsychotic drugs (neuroleptics)

Drugs	Mechanism of action	Advantages	Disadvantages	Examples
<p><b>First generation:</b> <b>Typical (older drugs)</b></p>	<ul style="list-style-type: none"> <li>Block D2 dopamine receptors: <b>high affinity (tight binding)</b></li> <li><u>Direct</u> ← receptor. irreversible → high adverse effect.</li> </ul>	<ul style="list-style-type: none"> <li>Effectively <u>treating</u> <u>positive symptoms</u> <u>+ve</u></li> </ul>	<ul style="list-style-type: none"> <li>Movement disorders (<u>extrapyramidal symptoms</u>).</li> <li><u>Negative symptoms NOT affected</u> <small>ما أثره على serotonin</small></li> <li><u>Neuroleptic malignant syndrome</u> <small>Fatal</small></li> </ul>	<ul style="list-style-type: none"> <li><u>Haloperidol</u></li> <li><u>Chlorpromazine</u></li> <li><u>Fluphenazine</u>.</li> </ul>
<p><b>2<sup>nd</sup> generation:</b> <b>Atypical (newer drugs)</b></p>	<ul style="list-style-type: none"> <li>Block dopamine D2 and serotonin 2A receptors (5HT2A): <b>less affinity to dopamine receptors (loose binding)</b></li> </ul>	<ul style="list-style-type: none"> <li><b>Better for negative symptoms</b> <small>serotonin block</small></li> <li><b>Extrapyramidal symptoms</b> : <b>less risk</b> <small>loos binding</small></li> <li>Less risk of <b>hyperprolactinemia</b></li> <li>Less non-compliance</li> <li>Reduce relapse <small>اكثر التراجع</small></li> </ul>	<ul style="list-style-type: none"> <li><b>Metabolic side effect</b></li> <li><b>Positive symptoms less affected</b></li> </ul>	<ul style="list-style-type: none"> <li><u>Risperidone</u></li> <li><u>Olanzapine</u></li> <li><u>Quetiapine</u></li> <li><u>Clozapine</u></li> </ul>
<p><b>Dopamine partial agonists (DAPAs)</b> <small>د ا ب ا</small> <b>Newest ones</b></p>	<ul style="list-style-type: none"> <li>Dopamine <small>(mixed agonist-antagonist)</small> partial agonist: increasing it when low and decreasing it when it is high</li> <li>High affinity D3&amp;2 receptors and serotonin:5-HT1A receptors.</li> </ul>	<ul style="list-style-type: none"> <li><u>Both positive and negative symptoms</u> are affected</li> </ul>	<ul style="list-style-type: none"> <li>Akathisia</li> <li>Sedation <small>دافع عايز بنام</small></li> </ul>	<ul style="list-style-type: none"> <li><u>Aripiprazole</u></li> <li><u>Cariprazine</u></li> </ul>

Typical is D<sub>2</sub> antagonist

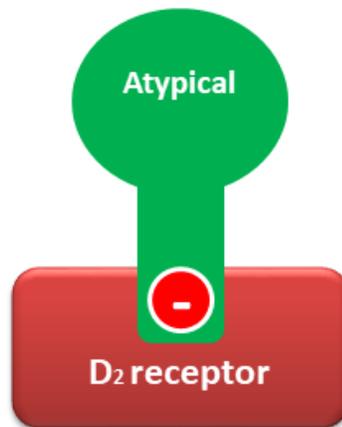
High affinity to D<sub>2</sub>



Binding to D<sub>2</sub> receptor  
(**tight**)

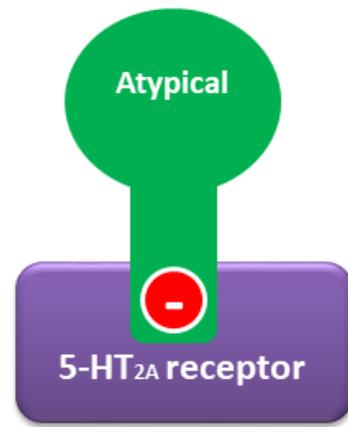
Atypical is serotonin-dopamine antagonist

Low affinity to D<sub>2</sub>



Binding to D<sub>2</sub> receptor  
(**loose**)

High affinity to 5-HT<sub>2A</sub>

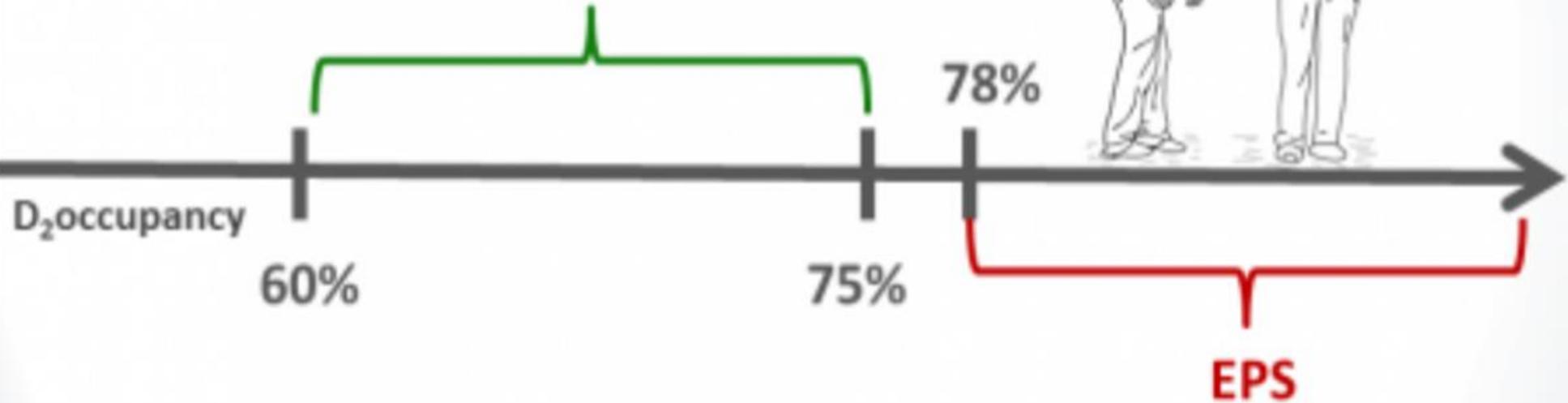


Atypical dissociate rapidly from D<sub>2</sub> receptor

# High D<sub>2</sub> Occupancy, High EPS Risk

↑ Affinity → ↑ Efficacy → ↑ Extrapyramidal Symptoms.

Antipsychotic efficacy



وجهة  
بداً

# Adverse effects of Antipsychotic drugs

## • 1- Extrapyramidal Symptoms (EPS) كل الاعراض على العضلات (movement)

• **Tremors** *Shaking movement.*

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

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

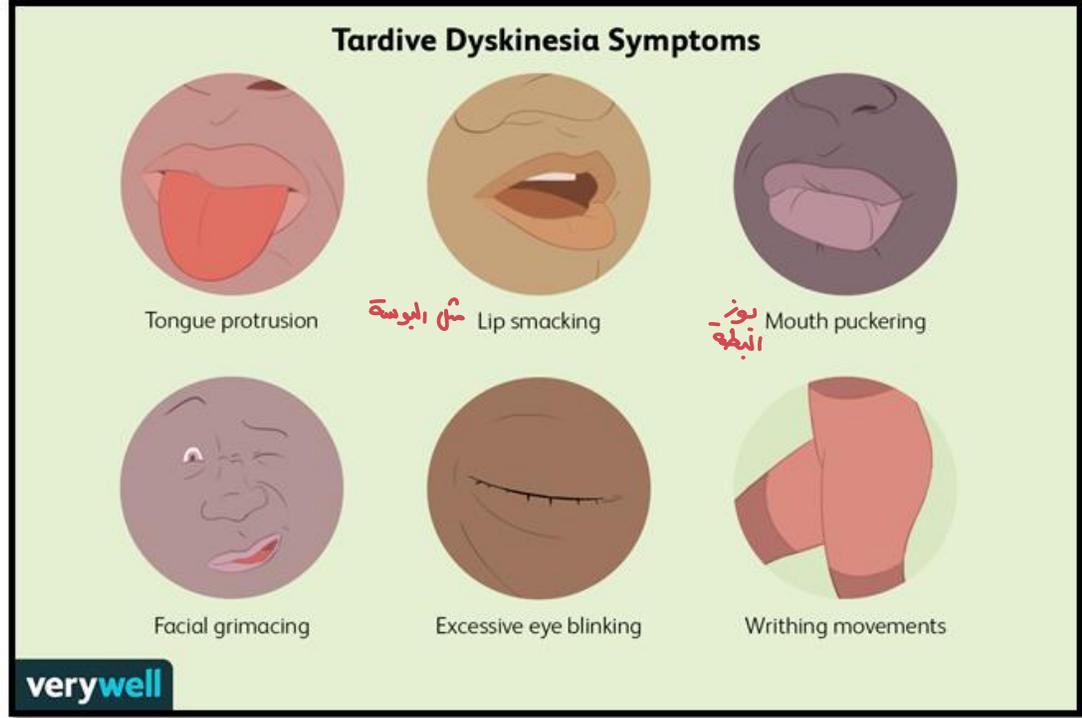
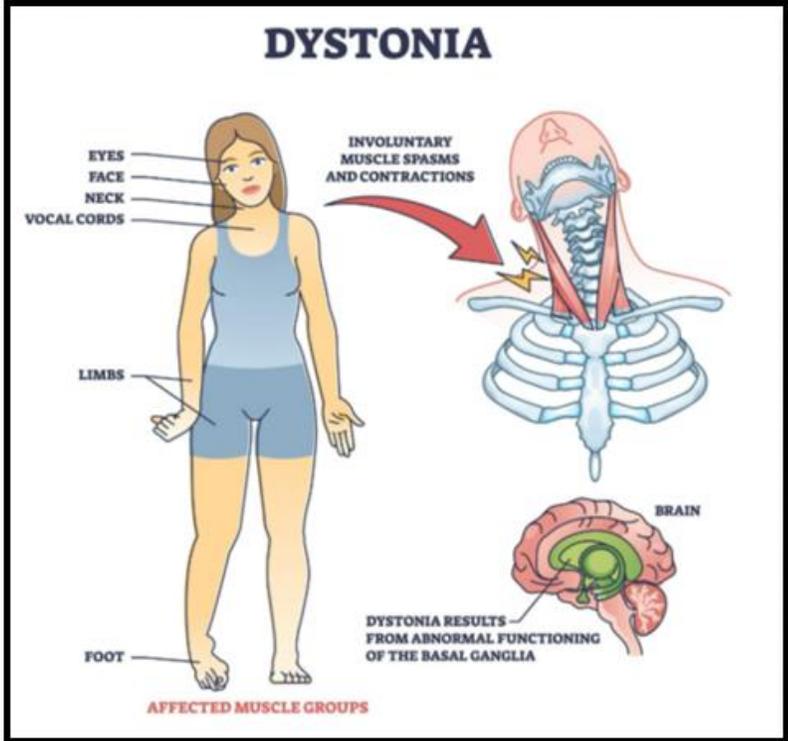
• **Treatment:** Anticholinergic drugs (e.g. benztropine slow IV) or

← Antihistaminics (e.g. diphenhydramine)  
Atropin like action.

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

First generation

# Extrapyramidal symptoms



# ADRs of Antipsychotic drugs

- **2- Akathisia:** احساس داخلي بعدم الراحة يؤدي للحركة. (احساس دائم)
- **Internal restlessness:** A deep, uncomfortable feeling of needing to move.
- **Fidgeting:** Shifting weight, swinging legs, pacing, or rocking. نظر بحركته .
- **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 #1 #3
- **Management:** dose reduction, switching drugs and benztropine



**Akathisia**



# ADRs of Antipsychotic Medications

# 1st .

## 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** زغلولة، لنا شفة
- **More prominent with first generation**

# ADRs of Antipsychotic Medications

## 5- Endocrinal disturbances: **Hyperprolactinemia**

*male & female*

Amenorrhea, menstrual cycle disorders, breast enlargement, galactorrhea

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

# ADRs of Antipsychotic Medications

## 6- Polyphagia: *multiple eating* *سراقة*

- Weight Gain and Metabolic Syndrome:
- Due to blocking of 5HT<sub>2A</sub> receptors in satiety center.
- More with atypical drugs

*مركز الشبع مسكّر*

2nd gen.

# ADRs of Antipsychotic Medications

## 7- Hematological

① • **Mild leukopenia**: common

must keep monitoring by CBC to avoid them. (1,2)

② • **Agranulocytosis** and **neutropenia** infrequent: may be **fatal**

• **Management**: stop the drug

• **Highest risk** in clozapine, at beginning of treatment

معرض ال infection  
أكثر

## ADRs of Antipsychotic Medications

### • 8- CVS:

- Arrhythmias

- Orthostatic hypotension)

- Antipsychotic drugs with increased risk:

- Haloperidol, olanzapine, risperidone

### • 9- Cholestatic jaundice:

- chlorpromazine #1 gen

# 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  
postnatal

**To summarize....**

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

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**Thank you**