Pharmacology

Modified no. 8

🎀🦋 الكاتب: فرح عليّان و زينة أبو ذياب

🎀🦋 المدقق: ميس قشّوع و ريناس الخريسات

الدكتور: مالك زحلف

Antipsychotic drugs  

Color code

- Slides
- Doctor
- Additional info
- Important

❖ Flow of information in this lecture 🤗

1. Introduction to Schizophrenia (Definition, Causes and Symptoms).
2. Discussing Dopamine Theory of Schizophrenia.
3. Discussing the 2 categories of Antipsychotic drugs (typical and atypical).

بسم الله نبدأ

Let's begin by discussing schizophrenia, then we'll explore the medications that’s used to treat it in more details !

Schizophrenia

- Pathogenesis is unknown.
- Onset of schizophrenia is in the late teens – early ‘20s.
- Genetic predisposition -- Familial incidence.

Hereditary Influences may account for 10% of schizophrenia cases.

- Multiple genes are involved.
- Afflicts 1% of the population worldwide.
- A thought disorder

It’s a men disease , remember when we talked about depression, it was related to ladies more.

- **Patho-Pharmacology of Schizophrenia (Psychosis)** 🧬💊

- In our last lecture, we discussed **depression**, which is considered **a sign rather than a disease**. Depression is **more common in women**, with a **2:1 ratio** of women to men diagnosed.

But **schizophrenia is different**. Unlike depression, it is a **disease**, not just a symptom. It is also **more common in men**, affecting them **around age 21**, while in women, it typically appears later, around **age 28**.

- Schizophrenia **stays with the patient for life**, meaning it causes **real, lasting changes**,it's **not just a placebo effect**.

- **Is Schizophrenia Genetic?** 🧬
- The first big question is: **Is schizophrenia, bipolar mania caused by genetics, or is there something else behind it?**

- Patients with schizophrenia may have **predisposing risk genes**, but **the disease itself is NOT purely genetic**. If schizophrenia were a genetic disease, a mutation (like a **single nucleotide polymorphism, duplication, or deletion**) would mean that the patient automatically develops the disease,but **that's not the case**. **Evidence?** 👉 **Identical twins** share the same genetic sequence, but one may develop schizophrenia while the other does not.

- Even though schizophrenia **runs in families**, this is due to **germline mutations** (mutations inherited from parents). **However, this is only a risk factor, not necessarily** that someone will develop the disease.

- **So, What Causes Schizophrenia?** 🌍

The **main cause** of schizophrenia is **environmental factors**, but with a genetic background like asthma, DM, hypertension . ودواليه ✨

- Environmental factors trigger **epigenetic changes**, such as **DNA methylation**, histone modification and posts translation modification which **permanently alters gene expression** (the disease is for life).

- **Chronic stress** plays a key role, it modifies genes in a way that **makes schizophrenia lifelong**.

Once these changes occur, **they cannot be reversed**, which is why stopping medication often leads to relapse.

Final Message : 👉

Schizophrenia is **not purely genetic**. It is an **environmental disorder with a genetic predisposition**. **No one is born destined to have schizophrenia**, it develops due to a combination of **risk genes and environmental influences.**

Schizophrenia

- Drugs currently used in the prevention of psychosis.

****These drugs are not a cure ****

- Schizophrenics must be treated with medications indefinitely, in as much as the disease in lifelong and it is preferable to prevent the psychotic episodes than to treat them.

SCHIZOPHRENIA IS FOR LIFE

There is no remission

There is always a relapse, when stopping the drug there is a relapse.

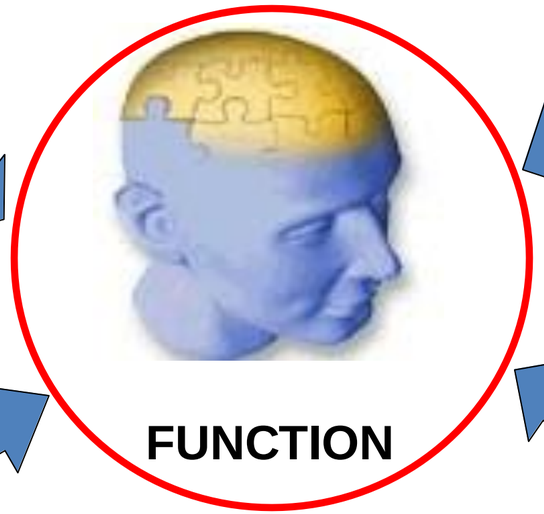
Schizophrenia - symptoms

Positive Symptoms
Hallucinations
Delusions (bizarre, persecutory)
Disorganized Thought
Perception disturbances
Inappropriate emotions

Positive symptoms: These are symptoms that add something to a person's normal experience, meaning they involve excesses or distortions of normal functions. These symptoms include things like hallucinations (hearing or seeing things that aren't there)

Negative Symptoms
Blunted emotions
Anhedonia
Lack of feeling

Negative symptoms: These refer to a reduction or loss of normal functioning or abilities. They reflect a decrease in the ability to function in daily life.



Cognition
New Learning
Memory

Mood Symptoms
Loss of motivation
Social withdrawal
Insight
Demoralization
Suicide

Symptoms of Schizophrenia 😟

Schizophrenia symptoms can be categorized into **positive, negative, cognitive, mood, and movement-related symptoms**. The underlying mechanism involves an **increase in dopaminergic activity** within the brain, leading to different types of symptoms:

1. Positive Symptoms:

- The **first symptoms** observed in a schizophrenia patient are **positive symptoms**, which include:
Hallucinations, **Delusions**, **Disorganized thoughts**, **Perception disturbances and inappropriate emotions.**

- The patient may struggle to form a single sentence or link sentences together. They may say things that confuse the listener and imagine or see things that do not exist.

2. Negative Symptoms:

- The **main problem** in schizophrenia is **negative symptoms**, which include:
Blunted emotions, **Anhedonia (inability to feel pleasure)**, **Lack of feeling.**

- The theory suggests that when **dopamine** increases, **serotonin** levels decrease in the **substantia nigra**, leading to **depression, lack of motivation, and emotional blunting** (inhibition of serotonin activity).

3. Movement-Related Symptoms:

- The **limbic cortex**, which controls movement, is affected due to **dopamine hyperactivity**, leading to:
Akathisia (restlessness, inability to stay still),Akinesia (reduced movement),Excessive and fast movements
Since **dopamine controls motor movement**, its increase results in these motor disturbances.

4. Prolactin and Sexual Disturbances:

- High dopamine levels **suppress prolactin release**, leading to **sexual disturbances in males**.

5. Cognitive and Mood Symptoms:

- In addition to the above, schizophrenia also presents with **cognitive impairments and mood disturbances**.

○ Conclusion:

Given the symptoms and the role of dopamine, the logical approach to treatment is to **suppress dopamine activity**

إِنّ الخيول  وإن تراها أُرهِقَت سَيثورُ منها من يكون أَصِيلا

حتّى وإن حجَبَ الغبارُ عدوها تسمع لها عند اللقاء صهيلا

Extra Explanation!!

How can Akathisia and Akinthisia happen ?!

1. Akathisia (Restlessness) in Schizophrenia

• **High dopamine** activity, especially in areas like the **mesolimbic pathway**, can lead to **hyperactivity** and **restlessness**.

• In schizophrenia, **dopamine overactivity** in the **limbic system** (which regulates emotions and movement) leads to **agitation** and a feeling of **inner restlessness**, which is characteristic of akathisia.

• **Akathisia** often results in the person feeling compelled to **move constantly**—whether it's pacing, fidgeting, or shifting positions.

2. Akinesia (Reduced Movement) in Schizophrenia

• **Akinesia** in schizophrenia can still occur due to **dopamine dysregulation**, even though dopamine is **overall high in** the brain. This happens because the **dopamine system** is complex and has different pathways that regulate movement.

• **High dopamine** in certain parts of the brain, like the **mesolimbic** areas, causes symptoms like **hallucinations and delusions**, but in other areas such as the **nigrostriatal pathway** (which controls movement), the **dopamine system may be disrupted** or the dopamine receptors may become **desensitized**

Dopamine Theory of Schizophrenia

Many lines of evidence point to the aberrant **increased activity of the dopaminergic system as being critical in the symptomatology of schizophrenia**.

There is a greater occupancy of D2 receptors by dopamine => greater dopaminergic stimulation

Now, let's discuss the 2 categories of Antipsychotic drugs in general 💊 💊

Schizophrenia Pathophysiology

	Schizophrenia Pathophysiology :	Pharmacologic Profile of APDs :	
Past	**Excess dopaminergic activity**	**Dopamine antagonists**	(D_2-receptor)
Present	**Renewed interest in the role of serotonin (5-HT)**	**Combined antagonists**	($5\text{-}HT_2/D_2$)

The role of seretonin in schizophrenia:

There is growing evidence that serotonin and dopamine systems interact in the brain. For example, serotonin receptors (especially the 5-HT2A receptor) are involved in modulating dopamine release, and drugs that target serotonin receptors (such as atypical antipsychotics) are often used to treat schizophrenia.

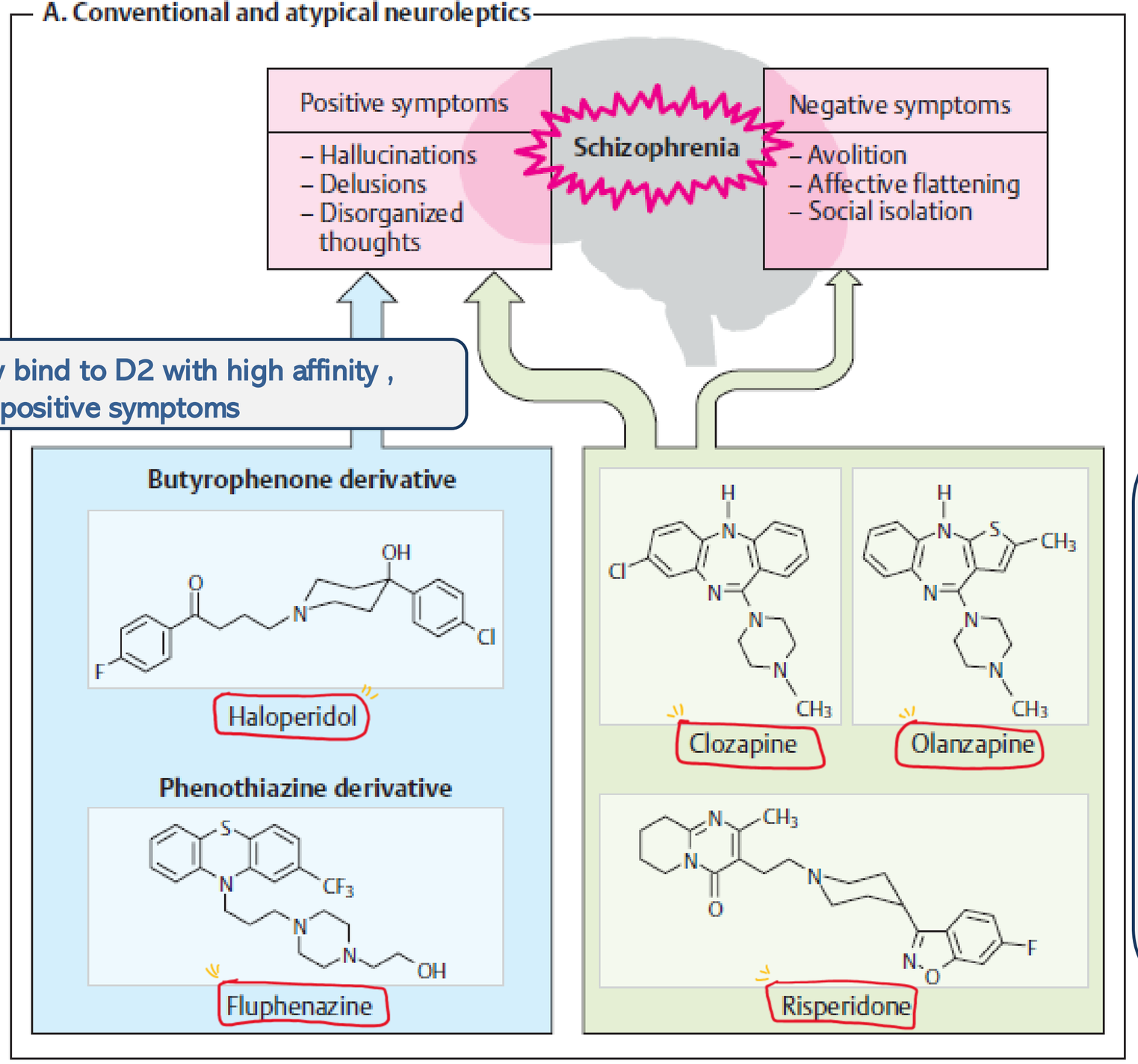
- **There are 2 main categories of antipsychotic drugs :**

1. Typical Drugs (D2 Antagonists): These drugs **only** target **dopamine receptors (D2),** specifically addressing the **positive symptoms** (e.g., hallucinations, delusions) of schizophrenia.

2. Atypical Drugs (New Generation): These drugs **target both D2 (dopamine) and 5HT2 (serotonin) receptors.** The dual action makes them effective against both **positive and negative symptoms** of schizophrenia (e.g., flat affect, social withdrawal).

- In the past, we were only dealing with suppressing dopamine, However, recently the new drugs of schizophrenia are dealing with **both** Dopamine and serotonin.

- Note : Serotonin Receptors and Depression: In cases of depression, an increase in **5HT2A receptors** can lead to symptoms of depression, independent of serotonin levels. This is a critical distinction since receptor density, rather than serotonin itself, may contribute to mood disorders.



Typical drugs , they bind to D2 with high affinity , They work only on positive symptoms

The best of typical drugs binds only to D2.

A weaker typical drug, which might bind also to alpha 1 receptor.

- Atypical drugs (new generation) , designed to address both positive and negative symptoms of schizophrenia. These drugs primarily target the D2 receptor and serotonin receptors, particularly 5HT2A and 5HT2C

- **More about Atypical drugs:**

- Their **lower affinity for D2 receptors** means they **also bind to other receptors**, which can lead to a **broader range of side effects**.

- For example, drugs like **clozapine and olanzapine** have been associated with metabolic side effects, such as **diabetes**, due to their action on the **5HT2C** receptor, which plays a role in regulating insulin and serotonin levels.

- **Clozapine**, in particular, can cause severe blood-related side effects, including **pancytopenia and agranulocytosis.**

- **As these medications interact with multiple receptors, they lose some of their specificity, leading to an increased risk of adverse effects.**

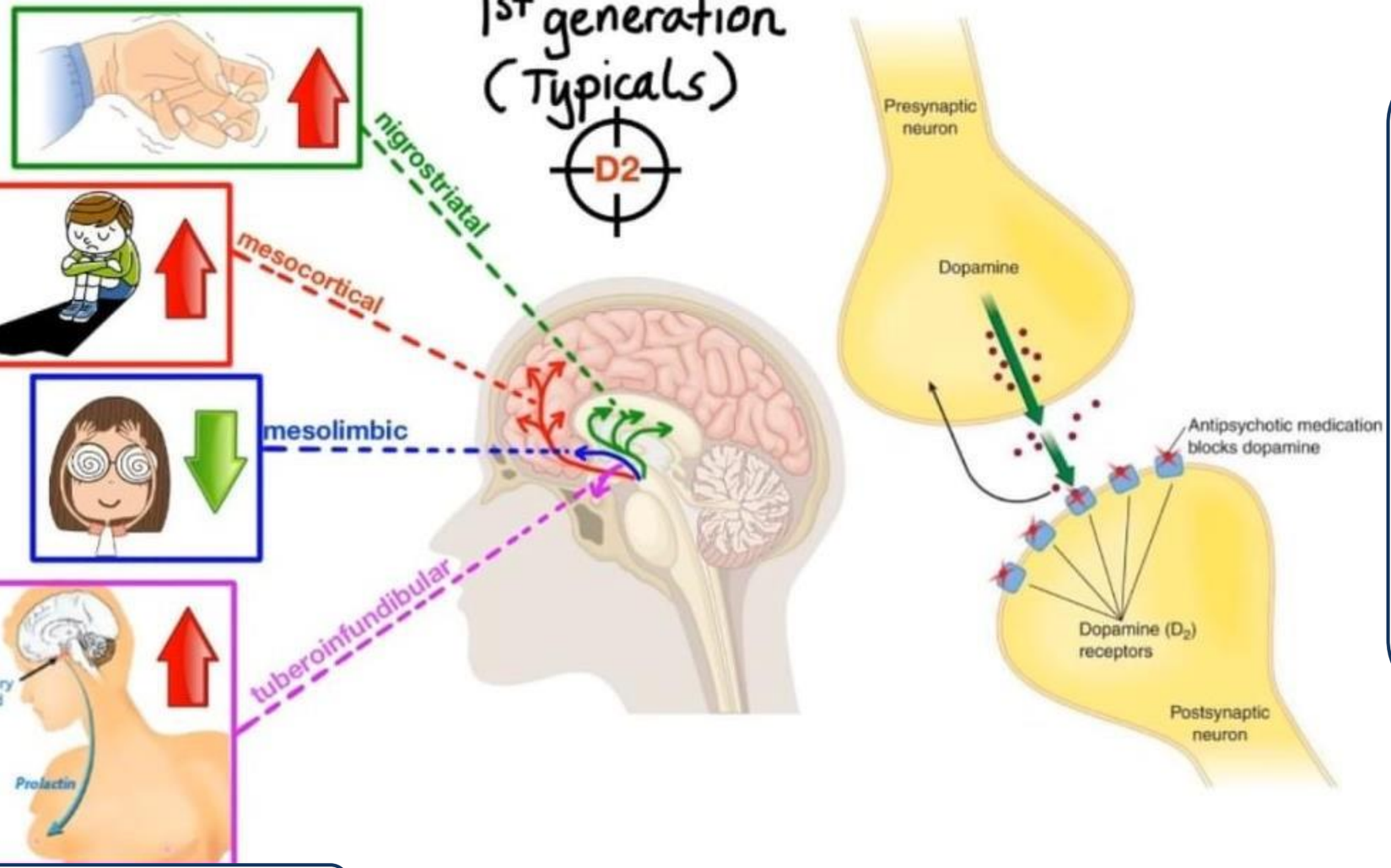
- **The effects of blocking Dopamine:**

- Reducing dopamine activity in mesocortical region > increases the feeling of sadness in patients.

Movement disturbance

Sadness

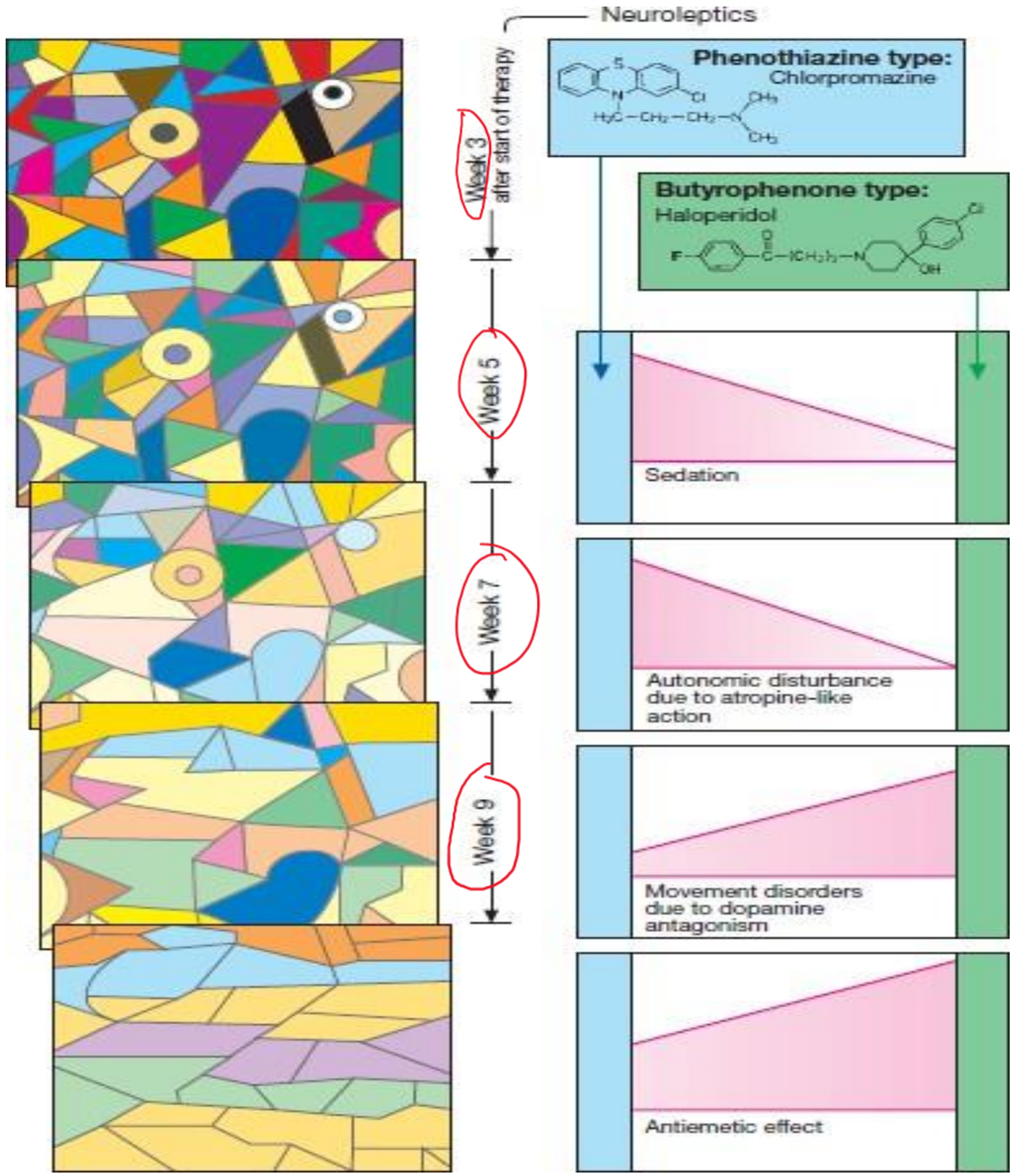
Delirium



D2 inhibition > increased prolactin production

- **So to sum up:**
- The typical drugs Have **intense** side effects due to strong D2 blockade.

- However , the atypical drugs have **more** side effects since they bind to many receptors due to their weak affinity towards D2.



- Both Typical and Atypical drugs need at least one week to produce their effect.
- However , they only need moments to produce the side effects (once they reach c max).
- So the patient must take these drugs for **long time,** since their effect in treating the abnormal thoughts is **gradual.**

The doctor skipped this slide

Tolerance and dependence to antipsychotic drugs

- Not addicting
- Relapse in psychosis if discontinued abruptly

- Tolerance develops to sedative effects
- No tolerance to antipsychotic effect

The doctor skipped this slide

Withdrawal-like syndrome

1. Symptoms: nausea, vomiting, insomnia, and headache
2. Symptoms may persist for up to 2 weeks.
3. Symptoms can be minimized with a tapered reduction of drug dosage.

Classification of Antipsychotic drugs

- Main categories are:
  - **Typical antipsychotics**
    - Phenothiazines : (**chlorpromazine, perphenazine, fluphenazine, thioridazine et al**).
    - Thioxanthenes : (**flupenthixol,clopenthixol**)
    - Butyrophenones : (**haloperidol, droperidol**)
  - **Atypical antipsychotics** (e.g. **clozapine, risperidone, sulpiride, olanzapine**)

The doctor emphasized on Haloperidol from the typical drugs.

Haloperidol , is an old drug .
It is given either **orally or through injections**
In case of **attacks** we use **injections.**

- The long time usage of haloperidol will cause the 4 extra pyramidal side effects (go to slide 22) , so we should continuously monitor the patient .

Classification of Antipsychotic drugs

- Distinction between ‘typical’ and ‘atypical’ groups is not clearly defined, but rests on:
  - Incidence of extrapyramidal side-effects (less in ‘atypical’ group)
  - Efficacy in treatment-resistant group of patients
  - Efficacy against negative symptoms.(atypical)

Now, let's start with First Generation Antipsychotic Drugs (Typical antipsychotics) 💊 🤩

First Generation Antipsychotic Drugs

Compound	Seda-tion	Hypo-tension	Motor (EP) Effects
Phenothiazines			
Chlorpromazine	+++	++	++
Fluphenazine	+	+	++++
Haloperidol	+	+	++++

Neurological Side Effects of antipsychotics

Important table

The extra pyramidal side effects of **Typical drugs** (when the drug is more specific to D2 these side effects will increase)

REACTION	FEATURES	TIME OF MAXIMAL RISK	PROPOSED MECHANISM	TREATMENT
Acute dystonia	Spasm of muscles of tongue, face, neck, back; may mimic seizures; *not* hysteria	1 to 5 days	Unknown	Antiparkinsonian agents are diagnostic and curative
Akathisia	Motor restlessness; *not* anxiety or "agitation" The patient keeps standing and cannot sit down.	5 to 60 days	Unknown	Reduce dose or change drug: antiparkinsonian agents, **benzodiazepines or propranololc** may help
Parkinsonism	Bradykinesia, rigidity, variable tremor, mask facies, shuffling gait	5 to 30 days	Antagonism of dopamine	Antiparkinsonian agents helpful
Tardive dyskinesia	Oral-facial dyskinesia; widespread choreoathetosis or dystonia	After months or years of treatment (worse on withdrawal)	Excess function of dopamine hypothesized	Prevention crucial; treatment unsatisfactory

The mechanism behind the side effects

In addition to D2 antagonist , to treat the side effects , so for example we give Haloperidol with antiParkinsonism drugs.

Tardive dyskinesia (فقدان الحركة اللاإرادي)

- Is a side effect associated with **long-term use** of dopamine antagonists, such as typical antipsychotics. This condition often manifests as **involuntary, repetitive movements**, like sending "fly kisses.“

- The underlying cause of these movements involves an **imbalance between acetylcholine (Ach) and dopamine in the brain**. Dopamine antagonists block dopamine receptors, leading to a compensatory **increase in the number of dopamine receptors over time**. This receptor upregulation makes the system **more sensitive to dopamine**, and when dopamine activity is suddenly increased or released, it results in **uncontrolled movements.**

- To manage tardive dyskinesia, treatment strategies often focus on **restoring balance, either by increasing acetylcholine activity or decreasing dopamine activity.**

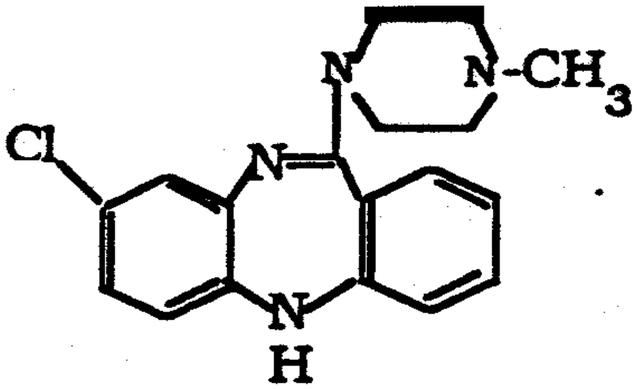
- **Reminder** : agonists decrease the number of receptors with prolonged use, antagonists lead to an increase in receptor density,

Now, let's start with Second Generation Antipsychotic Drugs (Atypical antipsychotics) 💊

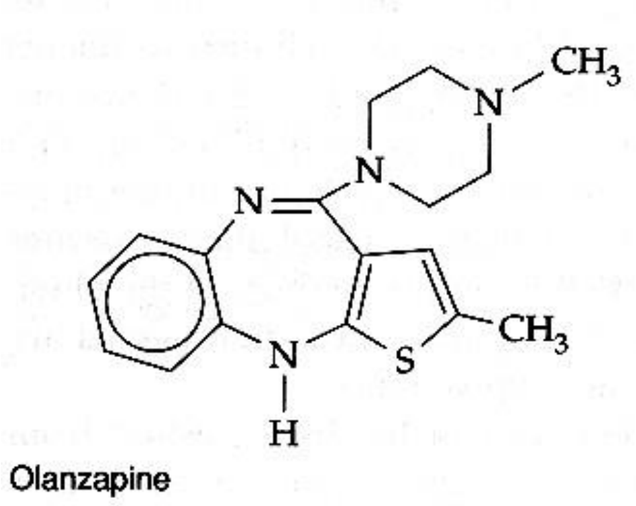
Second Generation Antipsychotic Drugs

Compound	Sedation	Hypo-tension	Motor effects
Risperidone Binding to H1 receptors will cause sedation. Binding to alpha 1 will cause orthostatic hypotension.	++	+++	+/++ Dose dependent
Clozapine And olanzapine They don't bind to D2 with a high affinity so they won't produce the extra pyramidal side effects.	++	++	-
Aripiprazole Partial agonist to all of the following: Alpha 1, H1, D2. Their partial antagonism won't produce strong side effects.	0/+	0/+	0/+

Clozapine and olanzapine



- VERY low EPS
- Blocks D1, D2, D4, α- adrenergic, 5HT2, muscarinic, and histamine H1 receptors
- May show greater efficacy against negative symptoms than other antipsychotic drugs
- **<u>Agranulocytosis is a potentially fatal side effect for clozapine</u>**



Olanzapine

Both drugs have high efficacy, but cause **significant <u>weight gain and diabetes</u>**

Risperidone

Endocrine effect

Risperidone has a high activity towards prolactin

- One of the most prescribed drugs in Jordan.
- In **women**, these disturbances include:
  - **galactorrhea**
  - **loss of libido**
  - delayed ovulation and menstruation or amenorrhea.

- In **men**, these disturbances include:
  - **gynecomastia**
  - **impotence.**

Quetiapine

Doesn't cause diabetes

- No increased risks for extrapyramidal symptoms
- Shares sedation, orthostatic hypotension, weight gain
- Does cause anticholinergic side effects– dry mouth, constipation
- **Does not elevate prolactin**

Ziprasidone - 2001

- **Similar to advantages of others, but argued not to cause weight gain**

Clozapine – 1.7 kg/month kg/month
Olanzipine – 2.3 kg/month kg/month

Quetiapine - 1.8 kg/month

Ziprasidone – 0.8

Risperidone – 1

Aripiprazole

- **Partial agonist at D2 receptor**
- Affinity for muscarinic, α_1-adrenergic, serotonin and histamine receptors
- Few extrapyramidal side effects
- **Weight gain** **feeling dizzy**

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Dosage adjustments - interactions

	Adjusted Dose
CYP2D6 Poor Metabolizers	
CYP2D6 Poor Metabolizers	300 mg
CYP2D6 Poor Metabolizers taking concomitant CYP3A4 inhibitors	200 mg
Patients Taking 400 mg of ABILIFY MAINTENA	
Strong CYP2D6 or CYP3A4 inhibitors	300 mg
CYP2D6 and CYP3A4 inhibitors	200 mg
CYP3A4 inducers	Avoid use
Patients Taking 300 mg of ABILIFY MAINTENA	
Strong CYP2D6 or CYP3A4 inhibitors	200 mg
CYP2D6 and CYP3A4 inhibitors	160 mg
CYP3A4 inducers	Avoid use

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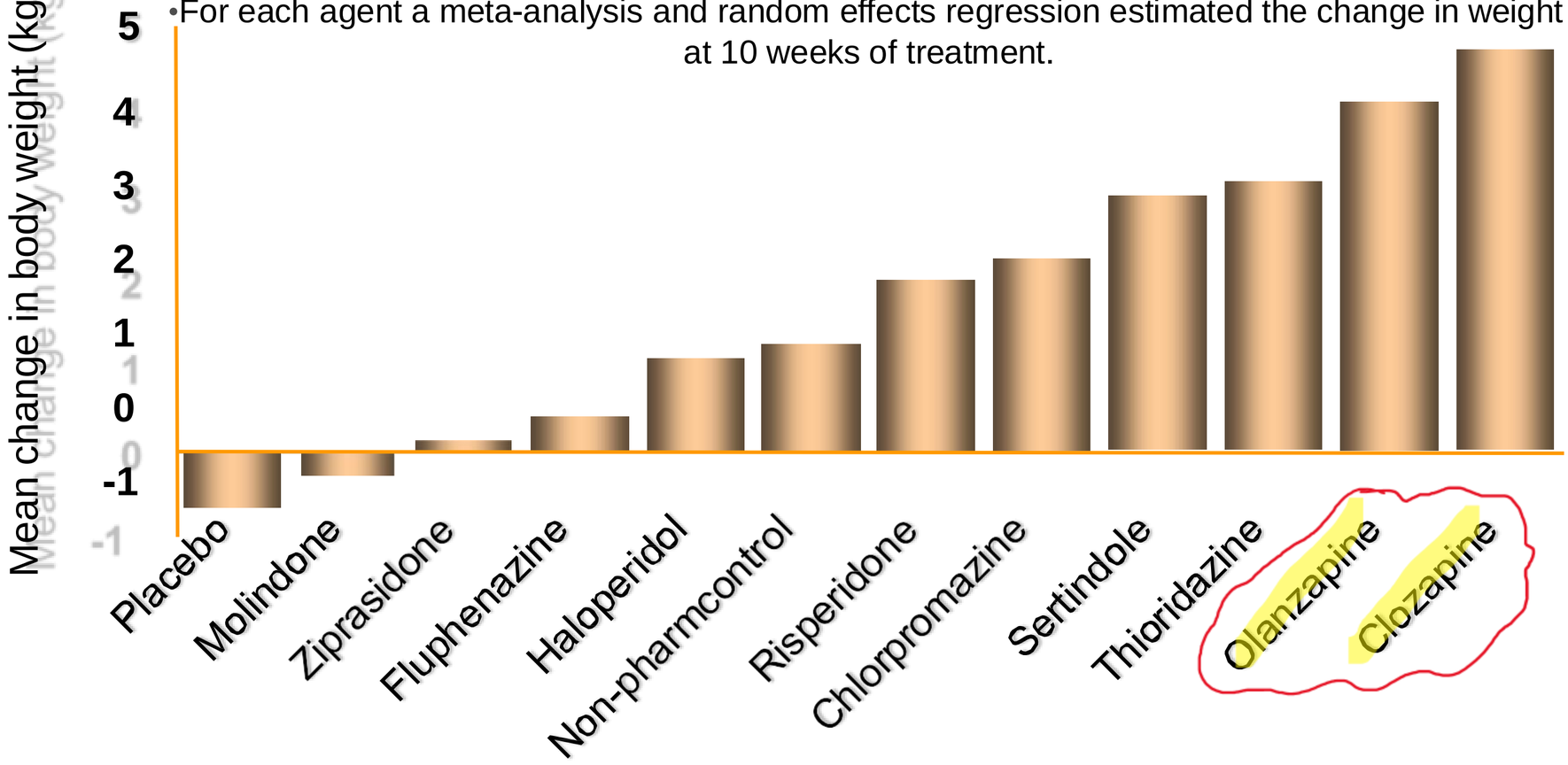
ESTIMATED MEAN WEIGHT GAIN AT 10 WEEKS

- A comprehensive literature search identified 78 studies that included data on weight change in patients treated with a specific antipsychotic.
- For each agent a meta-analysis and random effects regression estimated the change in weight at 10 weeks of treatment.



Allison DB, Mentore JL, Heo M, et al: Weight gain associated with conventional and newer antipsychotics: a meta Analysis. AJP, 1999.

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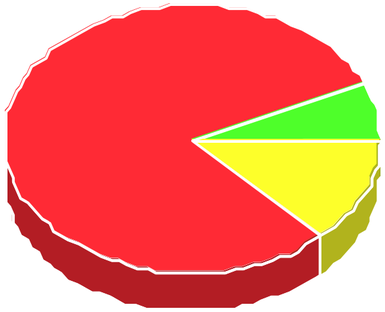
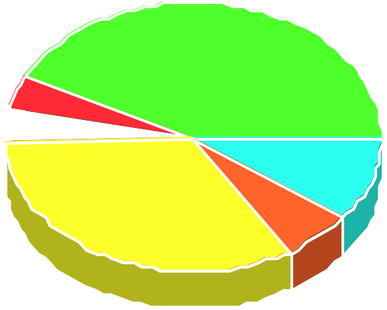
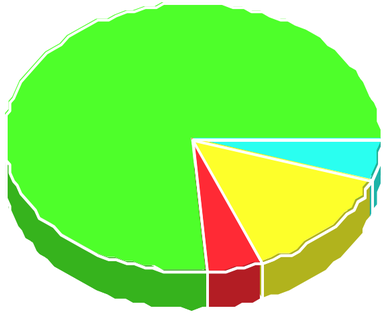
Atypical Antipsychotics In Vivo Binding Affinities



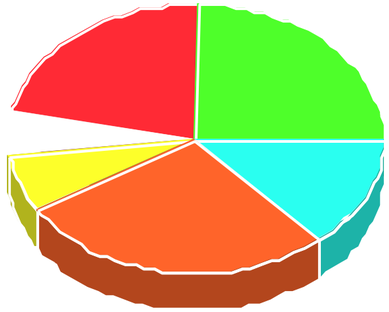
Haloperidol



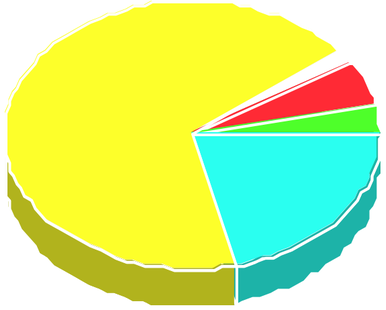
Clozapine



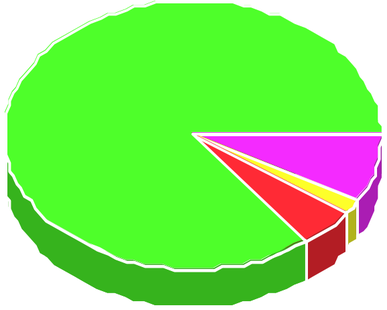
Risperidone



Olanzapine



Quetiapine



Ziprasidone

5HT2A D2 D1 Alpha1 Musc H1 5HT1A (agonist)

Casey 1994

إذا قَوِيَت هذه النَّفسُ بالإيمانِ أذَلَّتِ الدُّنيا، وإذا ضَعُفَتْ أذلَّتها الدُّنيا، الله أكبَرُ مِنَ الدَّنيا، الله أكبَرُ مِنَ الدُّنيا

VERSIONS	SLIDE #	BEFORE CORRECTION	AFTER CORRECTION
V1→ V2			
V2→V3			

امسح الرمز و شاركنا بأفكارك لتحسين أدائنا !!