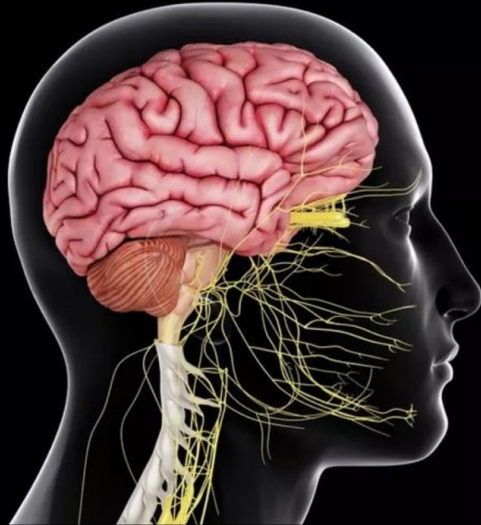


وَقُلْ رَبِّ زِدْنِي عِلْمًا



CENTRAL NERVOUS SYSTEM

SUBJECT : **Pharmacology**

LEC NO. : **Lec 5**

DONE BY : **Shefaa'almaaitah** ❤️

**FUTURE
DOCTOR**

Antipsychotic Drugs

=Neuroleptics, Major tranquilizers



تتركز دائما ال mental illness
Should combine both pharmacotherapy and psychotherapy
But we focus on the use of pharmacotreatment of these disorders

Definitions

Schizophrenia it's chronic psychotic illness that doesn't resolve on its own and it's most common form of psychosis
And characterized by persistent delusions and hallucinations in the absence of underlying cause

Not a mood disorder
No affect on mood like depression
thinking and personality and بل thought بل psychosis ال
behavior
يعني المشكلة غالبا هي بل With bizarre thinking or irrational thinking
perceptual thinking and personality

• **Psychosis:** Describe a group of mental illnesses

- Mental state involving detachment from the reality ↗

Madness; supernatural power

- **Diagnosis by exclusion** →

With psychosis usually we should eliminate any other reason that causes such abnormal behavior for establishing the diagnosis of psychosis
Especially most cases of psychosis not associated with underlining cause they just happen and we don't no why

For years psychosis associated with false description such as g

Main characteristic of these mental state is two main

① • **Delusion:** Proplem with thinking
بتفكر ب اشياء مش موجودة ب الواقع

False or bizarre fixed believes with no adequate evidence
اعتقادات عند المريض بدون دليل او صلة ب الواقع وثابتة وصعب تغيير قناعه المريض فيها

main symptom

② • **Hallucination** Proplem with sensation
تحس ب اشياء مش موجودة ب الواقع

For your knowledge
There are types of delusions
Such as Persecutory delusions (delusion of safety)
They are afraid and have ideas that someone harm them في حد بحاو
يقتلهم او يسممهم ب الاكل او يراقب تحركاته او يهدد وجوده
وهاد كلو ما اله صلة ب الواقع
google : Persecutory: People with this type of delusional disorder believe someone or something is mistreating, spying on or attempting to harm them (or someone close to them)

Sensory perception in the absence of external stimuli
Patient creat certain sensory images while they are actually absence
visual, auditory ممكن تكون
But most common form of hallucinations is auditory موجودة اشياء سببة عن المريض وفعليا هاي الاصوات مش موجودة
صوتات يسمعها بتحكى معاه وغالبا بتحكى اشياء سببة عن المريض وفعليا هاي الاصوات مش موجودة
ممكن تكون visual يعني بتخيل شخصية معينة وبحكي معها ويتفاعل معها

• **Illusions?** delusion عن نفرقتها عن مهم نكيتها عشان نفرقتها عن

not symptom of psychosis

To misperceive a stimulus
يعني ال stimulus موجود لكن انت تفهمه او تشوفه ب طريقة خاطئة
يعني مثلا واحد بتطلع ع شجرة ولكن هو يفكرها وحش يحاول يهجم عليه
في حين ال delusion انت بتخلق وجود شيء مش موجود



Psychosis: Causes

Poorly understood it's mixture of genetic and environmental factors

Schizophrenia primary psychotic illness runs in families and some environmental and developmental factors could play a role like childhood development of patient and environmental stress يمكن trigger psychosis and schizophrenia in patients who are predisposed to develop psychotic illnesses

Hallucinations may be due to withdrawal symptoms to quit alcohol or opioid

psychotic like presentation كل هاي ال drug ممكن تعمل
full blown psychosis بس ما بتسميها بهاي الحالة schizophrenia ولا بتسميها

Cannabis is a natural product, the main psychoactive constituent of which is tetrahydrocannabinol (THC)



- Genetic?
- Normal?
- Environmental
 - Stress

- **Drugs:**
 - ^{excessive} Alcohol; Cannabis
 - Cocaine; Amphetamine; MDMA From google Methyl enedioxy methamphetamine
 - K-opioid receptor agonists
 - NMDA Antagonists: Ketamine, Phencyclidine

Schizophrenic and psychosis with no underlying condition we say that diagnosis with elimination this means that we have other reversible secondary causes of psychosis

Medical conditions: Once you treat it a symptom goes away

- Alzheimer Later on could manifest with psychotic illness
- Brain tumors
- Infectious diseases: Viral encephalitis
- Electrolyte imbalance
- Fetal infections

Glutamate antagonist
 Could present with psychosis like symptoms
 role in antidepressant له بس هو أصلا anesthetic

طبعاً ما بتسميهم schizophrenia ب الحالة هاي لانه ال schizophrenia That happen with no underlying cause



Signs and symptoms

Classified as
Positive and negative
لكن مش معنى انهم مناخ ومش مناخ

• Positive

- Hallucination & delusions
- Thought disorders
- Abnormal behaviors (agitation, aggression, hostility)

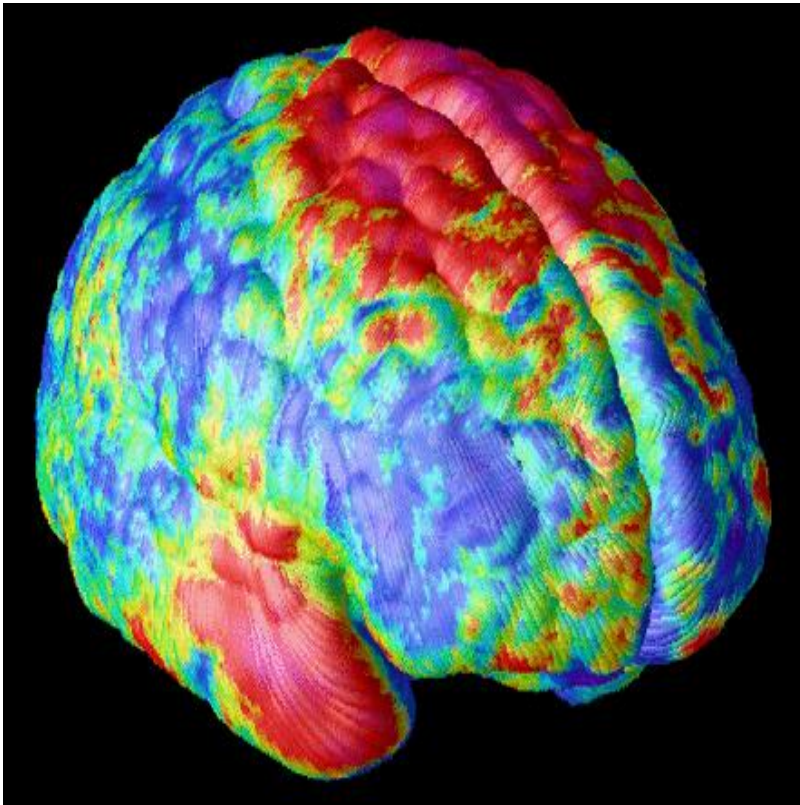
• Negative المهم علاقة ب ال mood

- Social contacts Antisocial
- Emotional responses Flattening of emotional responses
- Decrease attention and memory
- Anxiety and depression--→ Suicide

Higher than normal population for sure

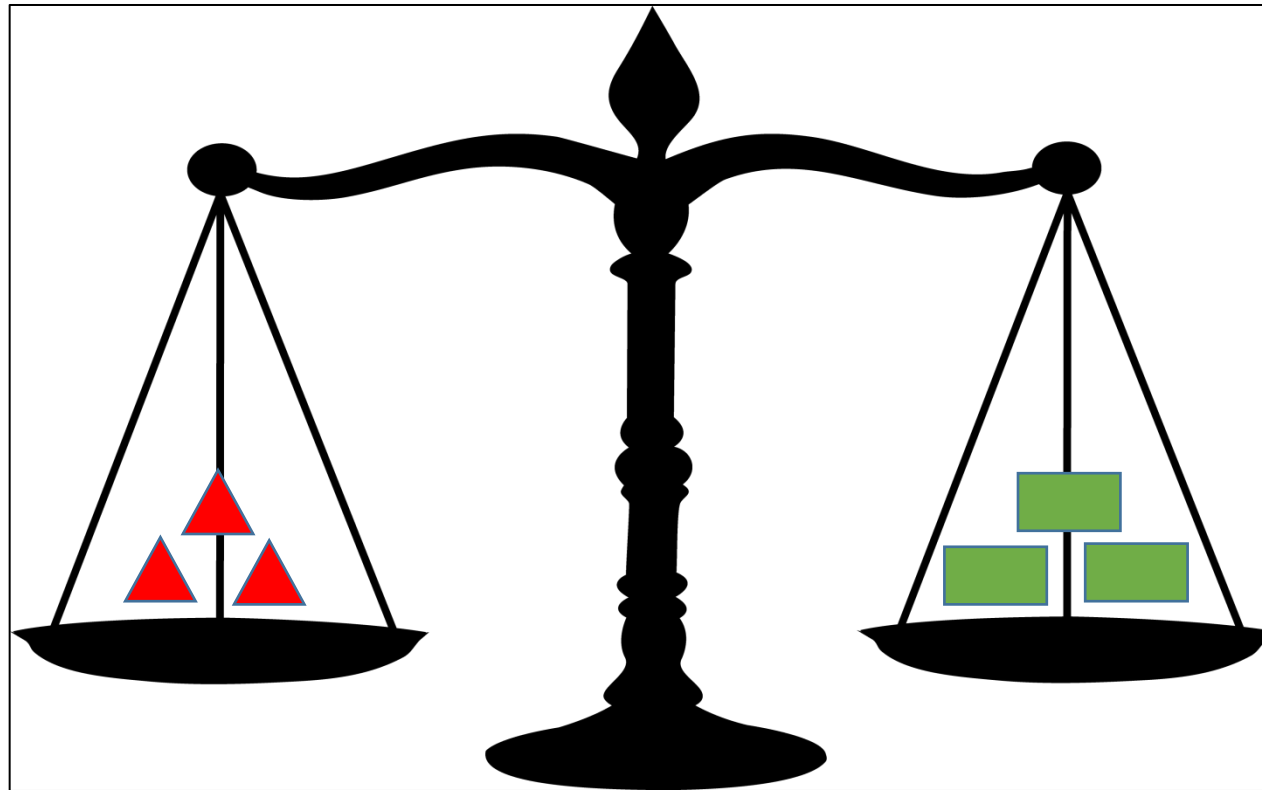
ويراك ترضى
وتصبر فيرضيك
بما تمنى

Psychosis: pathogenesis



Pathophysiology: Dopamine Hypothesis

Theories explain why psychosis happen basically rely on dopamine levels



Does the balance between Dopamine and glutamate is the cause

▲ Glutamate (Glu)

■ Dopamine (DA)





Dopamine

- A catecholamine neurotransmitter

- Projections:

الاماكن التي يطالع منها ال
functions of dopamine و

- Substantia Nigra:

One component where dopamine works in brain

- Basal Ganglia: Movement

هاد الجزء التي بخرّب ب parkinson disease

- Ventral tegmental area:

- Mesolimbic pathway: Reward and cognition

Learning and memory

- Arcuate nucleus:

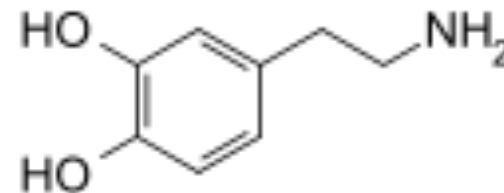
Activated by drug of abuse like opioids and CNS stimulants

- Pituitary gland: Inhibit prolactin secretion

- Receptors:

Dopamine is mixed inhibitory and excitatory NT
Depend on which type of receptor bind to it

- D 1,5 (Excitatory; Metabotropic; GPRC (Gs))
 - D 2, 3, 4 (Inhibitory; Metabotropic; GPCR (Gi))

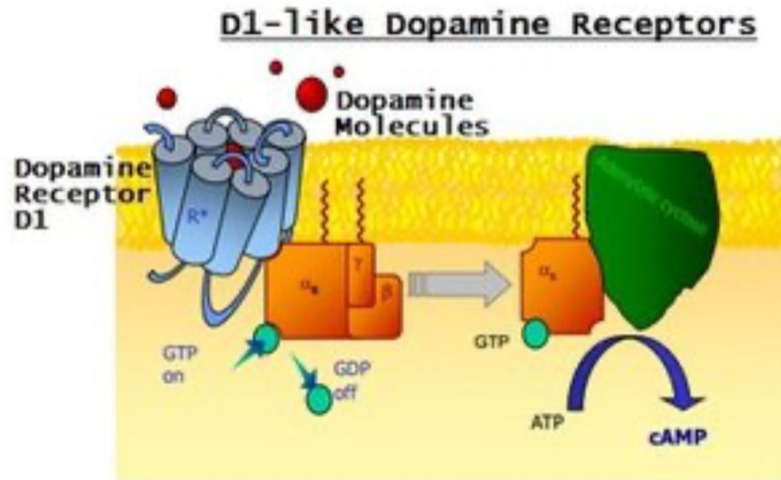


Theory that how dopamine play role in psychosis
Is basically has to do in balance between D1 and D2 brain functions

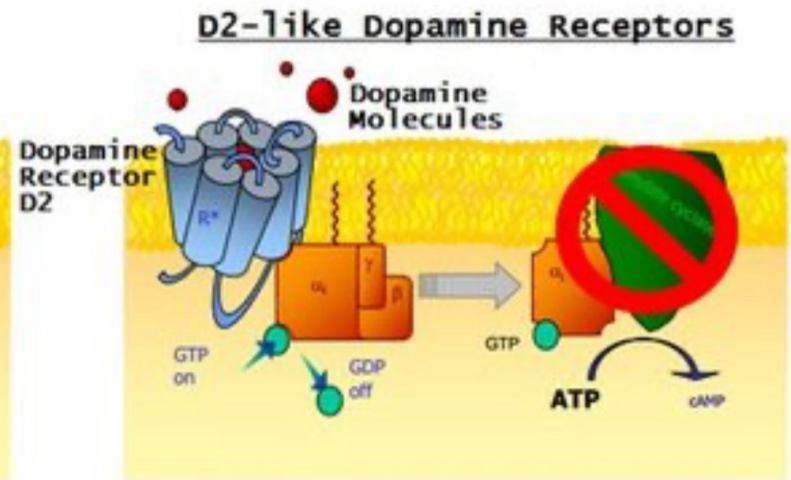
D1 vs. D2

D2 become now the main receptor that has
to do with MOA of most antipsychotic

D1-like Dopamine Receptors



D2-like Dopamine Receptors



Pathophysiology: Dopamine Hypothesis



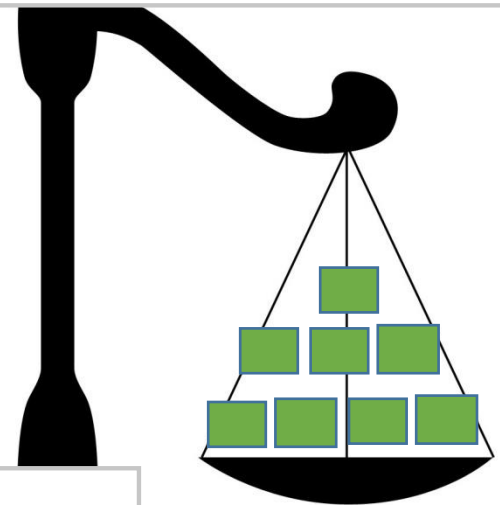
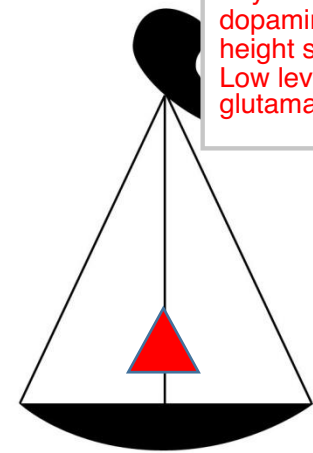
3
 هاي النظرية مش accurate في
 أشياء بتدعمها وفي أشياء بتخالفها
 لانها مش التفسير الحقيقي لل
 psychosis

Pros: *برعم*

- D2 agonists and dopamine releasers produce psychotic-like effects.
Drugs Amphetamine, bromocriptine
- Drugs block NMDA receptors produce psychotic-like effect.
 - Ketamine, Phencyclidine
- Antipsychotics are dopamine (D2) antagonists. *Successfully resolve most symptoms of psychosis*
 - Clozapine, Olanzapine

يعني لو واحد عنده psychosis
 ويباخد amphetamine ممكن
 يصيرله worse effects and
 increase hallucinations

1
 Psychosis is characterized by an imbalance between dopamine and glutamate
 height state of dopamine
 Low level of glutamate
 الحل هو تقليل ال dopamine وبيصير اقل من glutamate



Cons: *بخالف*

- Antipsychotics are not always effective.
- Therapeutic effect is generally delayed.
- Newer antipsychotics have 5-HT antagonistism (Pimavanserin)

2
 Where these drugs aim to lower dopamine level and maybe enhance glutamate level
 glutamate is excitotoxic ال بس ما بنعملها لانه ال
 الحل
 Most antipsychotic aimed at reducing dopamine
 dopamine receptor antagonist معظمهم عشان هيك هما

المفروض انهم antagonist dopamine immediately
 ليش ال symptoms بتطول حتى تتحسن
 ب التالي في other reasons in addition to
 dopamine imbalance

ب التالي في other NT الهم علاقة



 Dopamine



Antipsychotic Drugs: Principles

- The exact Pathophysiology is **not well understood.**
- Many people **do not respond fully** to medications or respond partially
- Therapeutic effect may be **delayed several weeks**

السبب

Significant side effects

السبب الرئيسي الهم هو non compliance
يعني to stop taking medication

They might require hospitalization until drug start to work

هم نقطة ب
المحاضرة

More effective against positive-symptoms

They have very weak effect on resolving
negative symptoms
يعني بعد العلاج ب ال antipsychotic حيا الهم ال
negative symptoms موجودين وهدول ما الهم علاج غير
cognitive behavioral and psychological
therapy

- Use the **minimum** effective dose.

Antipsychotic Drugs: Major S/E



Motor problems such as tardive dyskinesia that is irreversible effect and continue to happen
Characterized by Repetitive abnormal movement of facial muscles

• Hyperprolactinemia. →

- Galactorrhoea
- Gynecomastia

Specially in males

Because they are dopamine antagonists ب
التالي مافي اشني يثبط ال prolactin

• Sexual dysfunction: loss of libido.

• Neuroleptic malignant syndrome

• Tardive dyskinesia.

More severe side effect and life threatening
Characterized by shock high fever seizures
could kill the patient

• Sedation??

Impact life of patient
ممکن ما يقدر يصحى عل مدرسة او الجامعه

• Hyperglycemia and diabetes.

• Weight gain??

احد الاسباب الرئيسية لإيقاف استخدام هاي الادوية

Typical

Causes most patients quit taking these compounds

Atypical



Antipsychotic Drugs

Depend on their discovery
Not their efficacy

	Typical (First Generation)	Atypical (Second Generation)
<i>depend on</i> Discovery	Older	Newer
Effectiveness	Partially	Better? → <small>In resolving symptoms</small>
MOA	D2: Antagonist	<i>serotonin</i> D2: antagonist 5-HT: antagonist (5-HT3c)
* * Extrapiramidal S/E	+++++++	++ <i>less S/E</i>
		better <i>هاد الي خلاهم</i> And preferred to use

من ناحية efficacy في ناس
بحكو اه انهم احسن وفي ناس
بحكو لا



• The first neuroleptic (1952)

Associated with significant sedation

Typical

- Chlorpromazine
- Haloperidol

• Partial agonist at D2

D2 antagonists الباقيين كلهم

• Antiemetic with cancer chemotherapy

To reduce nausea and vomiting of cancer

It's injectable use in emergency to treat acute psychotic episode

• Decrease risk of suicide

Very effective antipsychotic

Correct positive symptoms

مشكلته انه associated with major AE one of them
كثير خطير
ب الإضافة إلى agranulocytosis

Atypical

- Clozapine
- Olanzapine
- Risperidone
- Ziprasidone
- Amisulpride
- Aripiprazole

clozapine يشبهه ال
less effective بس



Other Antipsychotics

- Pimavanserin:

- Approved in 2016.
- No dopamine action.
- 5-HT inverse agonist (i.e. antagonist)

- \$\$\$\$\$\$

Very expensive



To treat- Parkinson's disease psychosis.



Antipsychotics: Other uses

Other than psychosis



Bipolar

- Anxiety Disorders: OCD
- Huntington Disease
- Autism
- Antiemetic



Antipsychotic Drugs: Clinical notes

- Most are effective against positive symptoms.

The drug are affected by smoking

Smoking increase metabolism of Clozapine

- Change the medication

ازا الدواء ما اشتغل وما اعطى initial response او كان في response وبعد فترة صار في relapse

- Injectable forms:

لحد ما واحد فيهم يزيبط مع المريض ويرتاح عليه من ناحية SE
You should try with different antipsychotic

- Non-Compliance of the patient

ال non compliance هي المشكلة الرئيسية ومعظم المرضى ما بياخدو الدواء تاعهم او عندهم مشكلة انهم ياخدوه orally

- Acute psychotic agitation or mania

- Safe during pregnancy

Can still be used in pregnant lady

It always seems impossible until it's done.

Question 1



Question 2

• **Antipsychotics can produce all of the following except:**

- A. Hyperglycemia
- B. sedation
- C. Weight loss
- D. Sexual dysfunction
- E. It can produce all of the above

• **Examples of typical antipsychotics:**

- A. Olanzapine
- B. Haloperidol
- C. Clozapine
- D. Ziprasidone
- E. All of the above

Question 3

• **Dopamine (D1) receptors are:**

- A. Ionotropic excitatory
- B. Metabotropic excitatory
- C. Ionotropic Inhibitory
- D. Metabotropic inhibitory
- E. Voltage-gated receptors

Question 4

• **A patient look at a tea cup, and he claims it is a bomb. This is an example of:**

- A. Dillusion
- B. Illusion
- C. Hallucination
- D. Schizophrenia
- E. Sounds like normal to me!