

# Antipsychotic Drugs

=Neuroleptics, Major tranquilizers



# Definitions

- **Psychosis:**
  - Mental state involving detachment from the reality
  - Madness; supernatural power
  - Diagnosis by exclusion
- **Delusion:**
- **Hallucination:**
- **Illusions?**



# Psychosis: Causes

- Genetic?
- Normal?
- Environmental
  - Stress
- Medical conditions:
  - 
  - 
  - 
  - 
  -
- Drugs:
  - Alcohol; Cannabis
  - Cocaine; Amphetamine; MDMA
  - K-opioid receptor agonists
  - NMDA Antagonists:

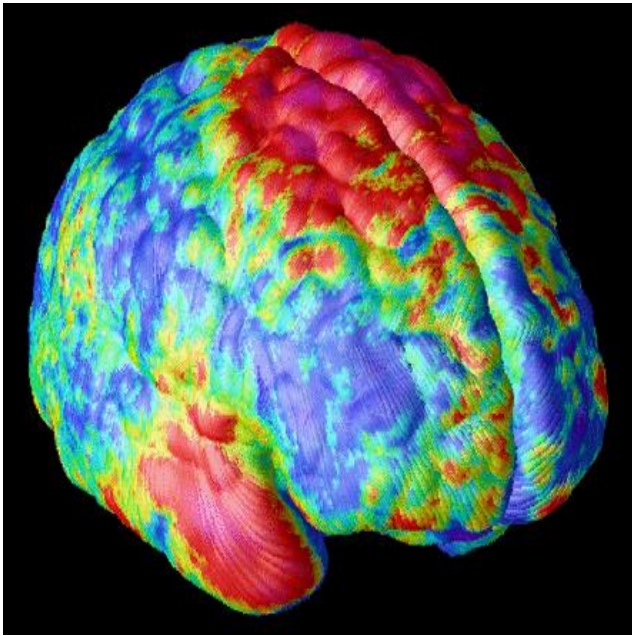


# Signs and symptoms

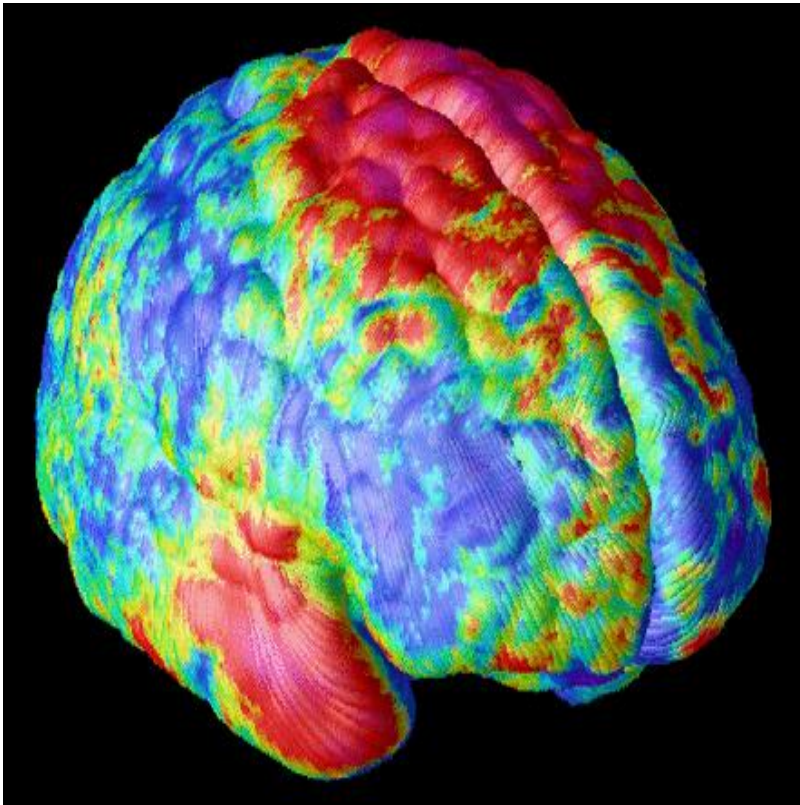
- Positive
  - Hallucination & delusions
  - Thought disorders
  - Abnormal behaviors
- Negative
  - Social contacts
  - Emotional responses
  - Decrease attention and memory
  - Anxiety and depression--→ Suicide



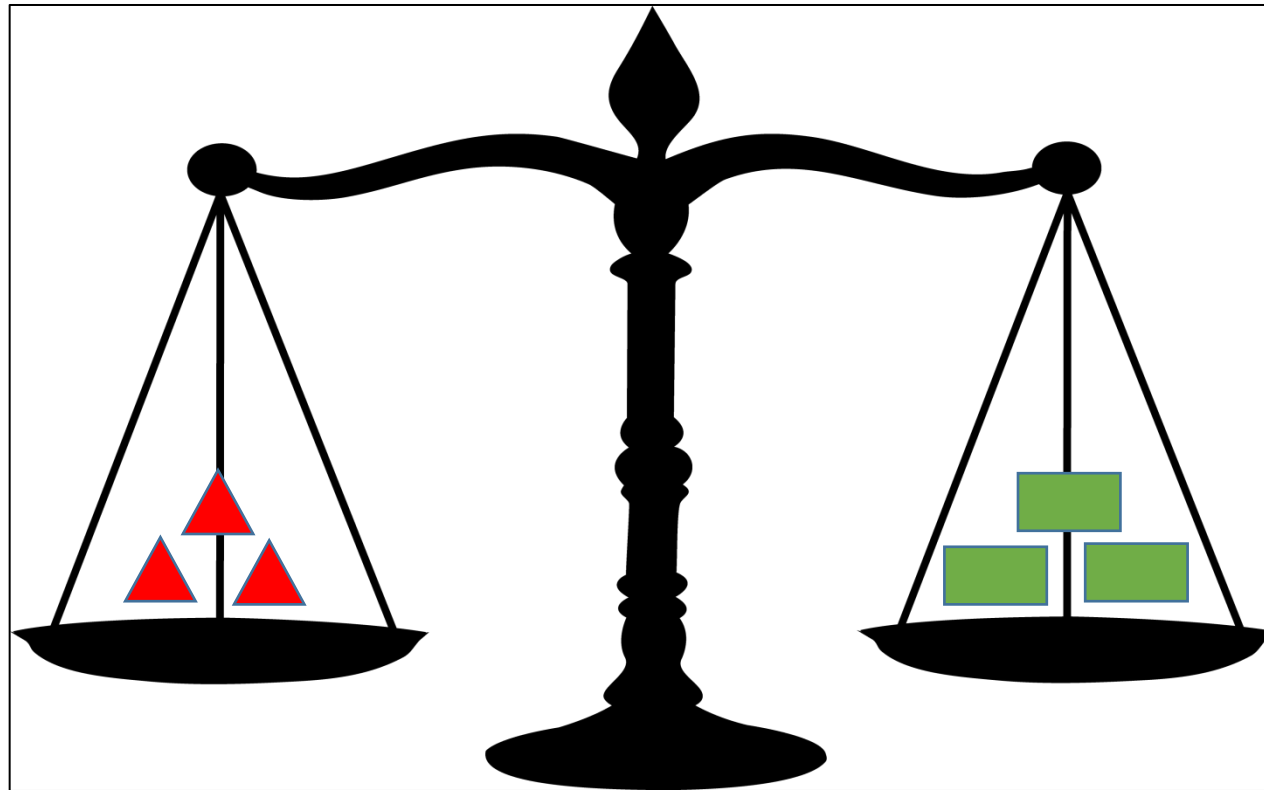
# Psychosis: pathogenesis



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# Pathophysiology: Dopamine Hypothesis



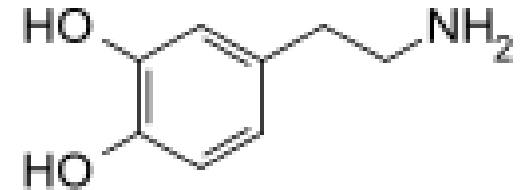
 **Glutamate (Glu)**

 **Dopamine (DA)**



# Dopamine

- A catecholamine neurotransmitter
- Projections:
  - Substantia Nigra:
    - Basal Ganglia: Movement
  - Ventral tegmental area:
    - Mesolimbic pathway: Reward and cognition
  - Arcuate nucleus:
    - Pituitary gland: Inhibit prolactin secretion
- Receptors:
  - D 1,5 (Excitatory; Metabotropic; GPRC (Gs))
  - D 2, 3, 4 (Inhibitory; Metabotropic; GPCR (Gi))





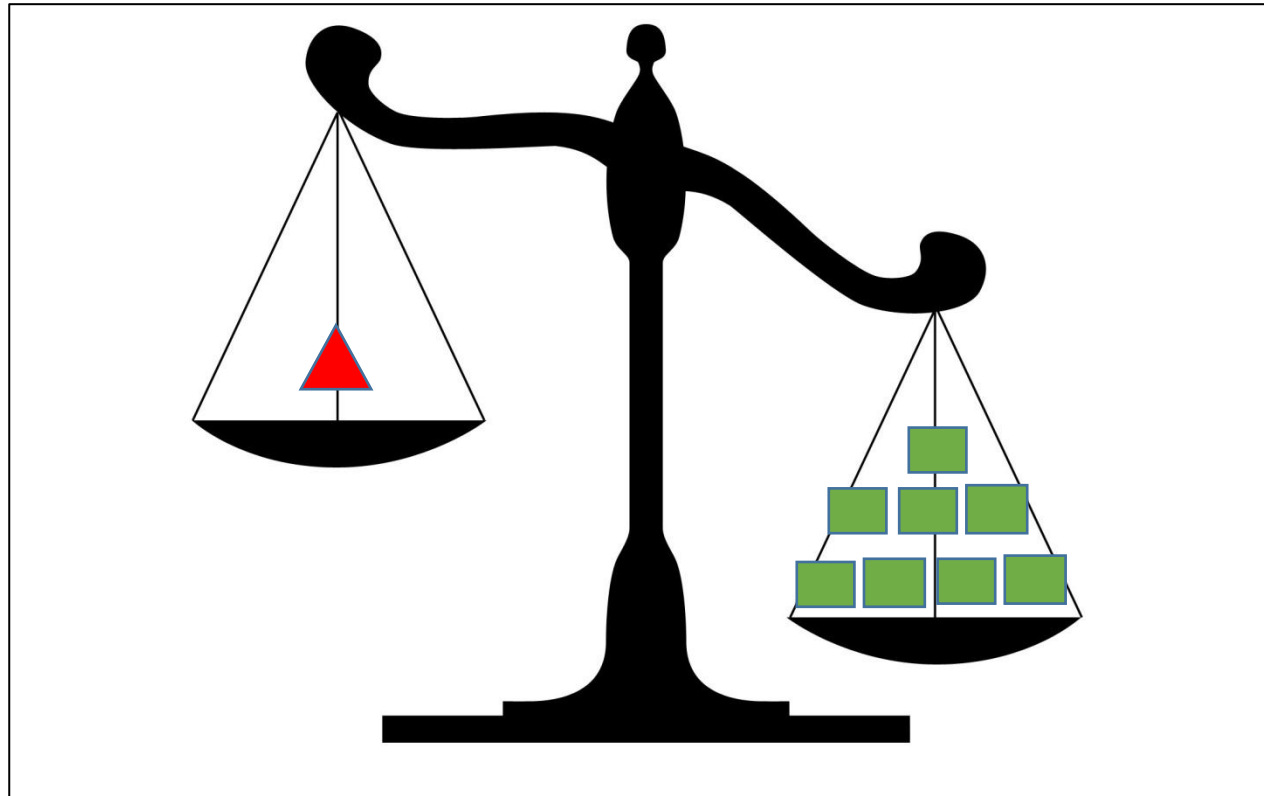
# D1 vs. D2

D1-like Dopamine Receptors

D2-like Dopamine Receptors



# Pathophysiology: Dopamine Hypothesis



 **Glutamate (Glu)**

 **Dopamine (DA)**



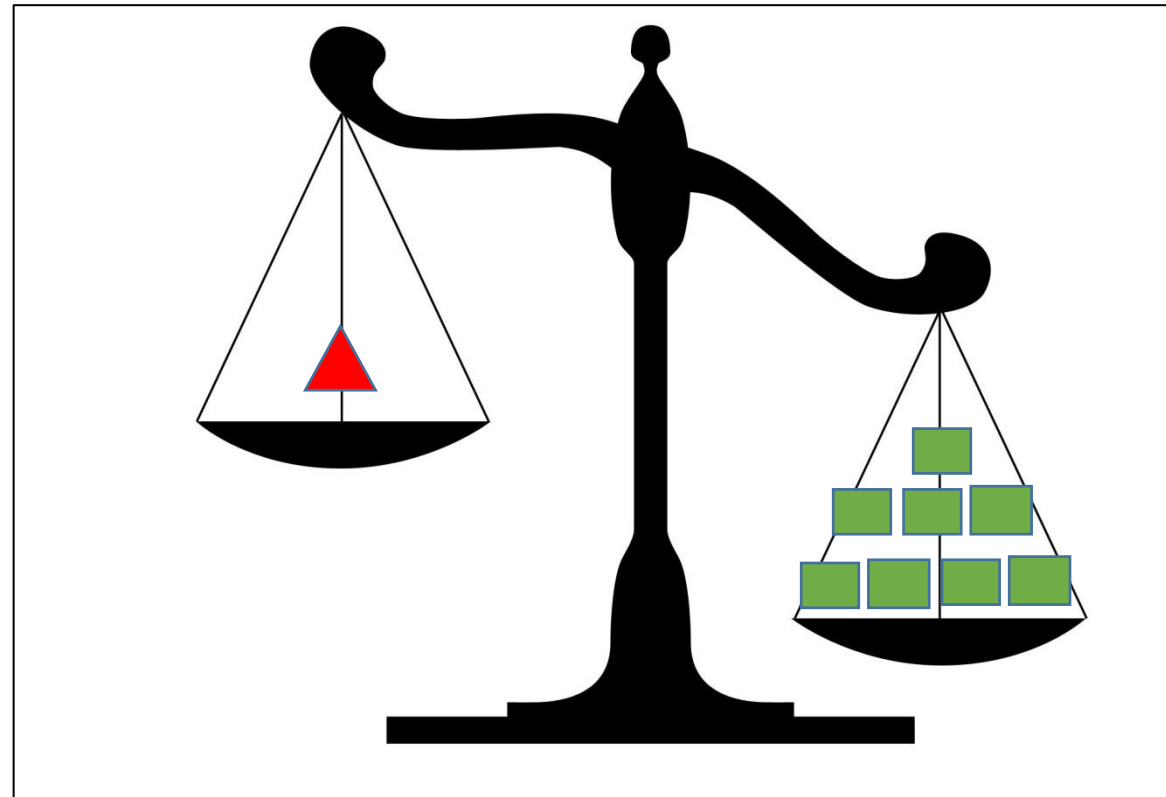
# Pathophysiology: Dopamine Hypothesis

## Pros:

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

## Cons:

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



**Glutamate (Glu)**



**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
- Significant side effects
- More effective against positive-symptoms
- Use the minimum effective dose.



# Antipsychotic Drugs: Major S/E

- Hyperprolactinemia.
  - Galactorrhoea
  - Gynecomastia
- Sexual dysfunction:
- Neuroleptic malignant syndrome
- Tardive dyskinesia.
- Sedation??
- Hyperglycemia and diabetes
- Weight gain??



# Antipsychotic Drugs: Major S/E

- Hyperprolactinemia.
  - Galactorrhoea
  - Gynecomastia
- Sexual dysfunction: loss of libido.
- Neuroleptic malignant syndrome
- Tardive dyskinesia.
- Sedation??
- **Hyperglycemia and diabetes.**
- Weight gain??

**Typical**

**Atypical**



# Antipsychotic Drugs

	<b>Typical (First Generation)</b>	<b>Atypical (Second Generation)</b>
Discovery	Older	Newer
Effectiveness	Partially	Better?
MOA	D2: Antagonist	D2: antagonist 5-HT: antagonist (5-HT3c)
Extrapyramidal S/E	+++++++	++



• The first neuroleptic (1952)

## Typical

- **Chlorpromazine**
- **Haloperidol**

• Partial agonist at D2

• Antiemetic with cancer chemotherapy

• Decrease risk of suicide

## Atypical

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





# Other Antipsychotics

- Pimavanserin:
  - Approved in 2016.
  - No dopamine action.
  - 5-HT inverse agonist (i.e. antagonist)
  - \$\$\$\$\$\$
  - Parkinson's disease psychosis.



# Antipsychotics: Other uses

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



# Antipsychotic Drugs: Clinical notes

- Most are effective against positive symptoms.
- Smoking increase metabolism of Clozapine
- Change the medication
- Injectable forms:
  - Non-Compliance of the patient
  - Acute psychotic agitation or mania
- Safe during pregnancy



Thank you



# Question 1

- **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

## Question 2

- **Examples of typical antipsychotics:**

- A. Olanzapine
- B. Haloperidol
- C. Clozapine
- D. Ziprazidone
- 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!