Antipsychotic Drugs

=Neuroleptics, Major tranquilizers

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Definitions

- Psychosis:
  - Mental state involving detachment from the reality
  - Change in personality and abnormal thoughts
  - Madness; supernatural power
  - Diagnosis by exclusion
- Delusion:
  - False beliefs with no adequate evidence
- Hallucination:
  - Sensory perception in the absence of external stimuli
    - Any sensation: mainly auditory
- Illusions?

Psychosis: Causes

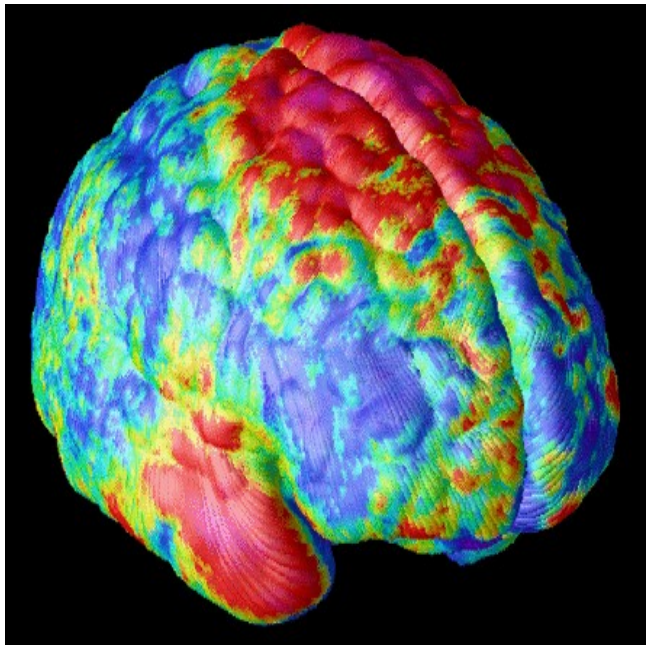
- Genetic?
- Normal?
- Environmental
  - Stress
- Medical conditions:
  - Alzheimer
  - Brain tumors
  - Infectious diseases:
    - Viral encephalitis
  - Electrolyte imbalance
  - Fetal infections

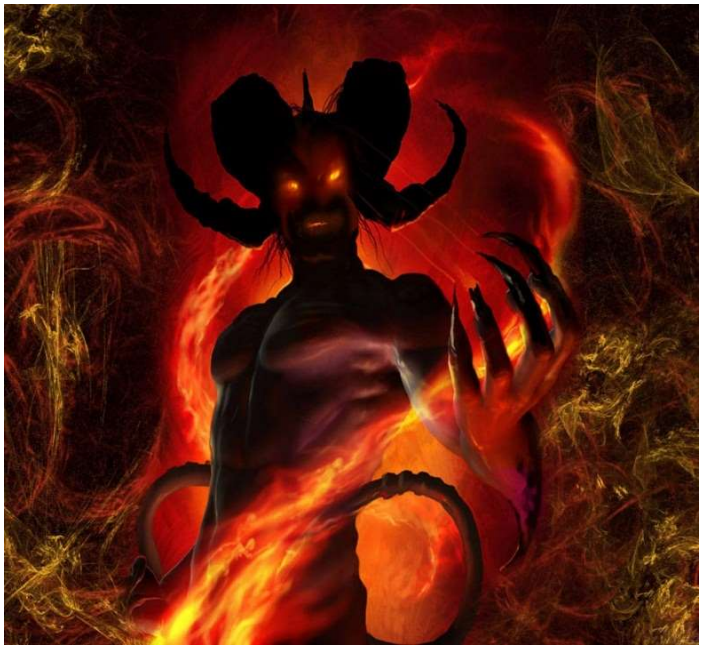
- Drugs:
  - Alcohol; Cannabis
  - Cocaine; Amphetamine; MDMA
  - K-opioid receptor agonists
  - NMDA Antagonists:
    Ketamine; Phencyclidine

Signs and symptoms

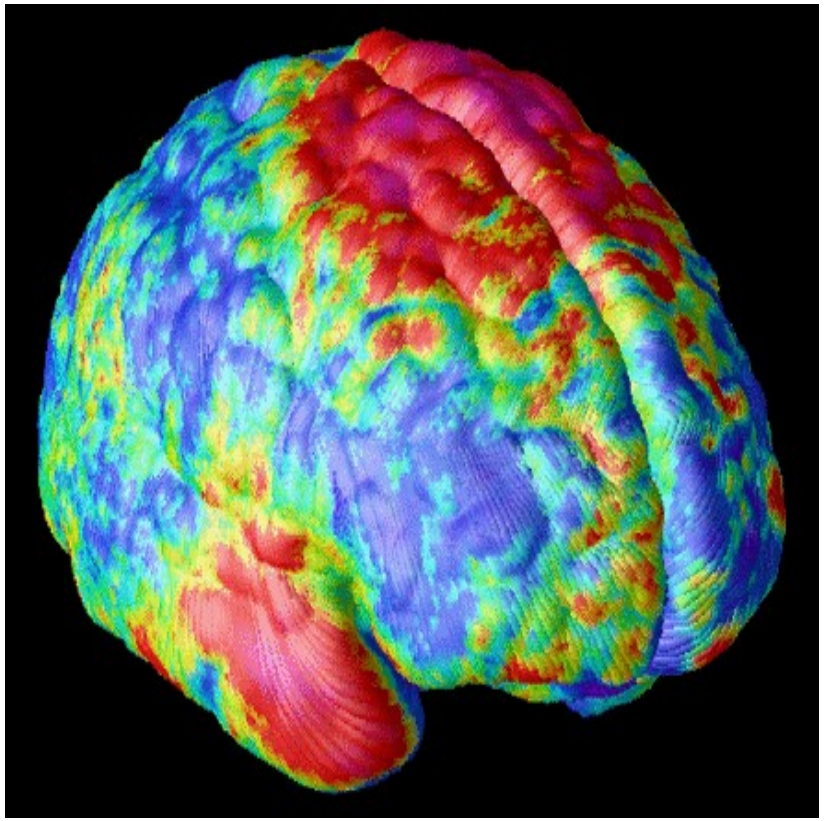
- Positive
  - Hallucination & delusions
  - Thought disorders
  - Abnormal behaviors (agitation, aggression, hostility, …)
- Negative
  - Withdrawal from social contacts
  - Flattening of emotional responses
  - Decrease attention and memory
  - Anxiety and depression--→ Suicide

Psychosis: pathogenesis

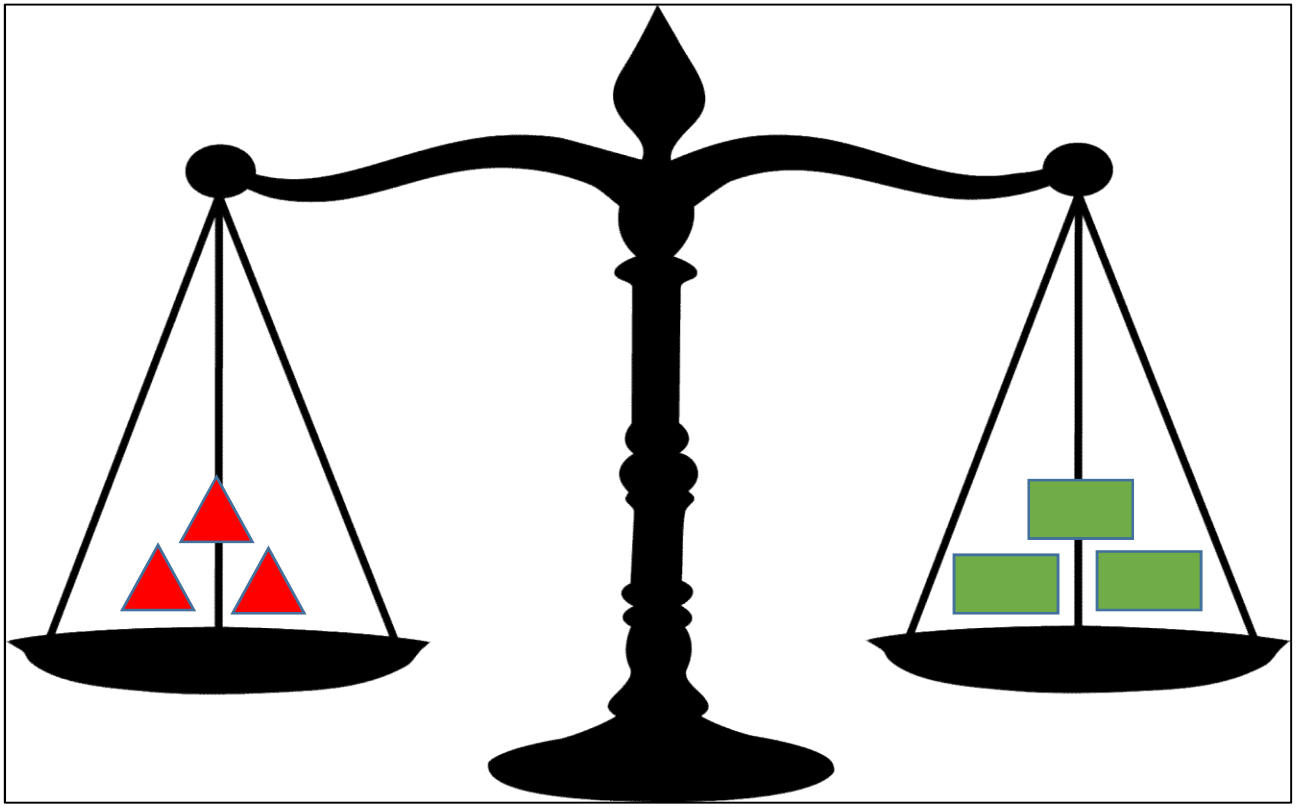




Psychosis: pathogenesis



Pathophysiology: Dopamine Hypothesis

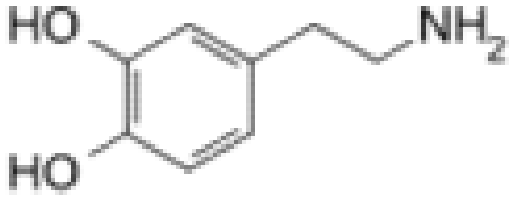


Glutamate (Glu)

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))

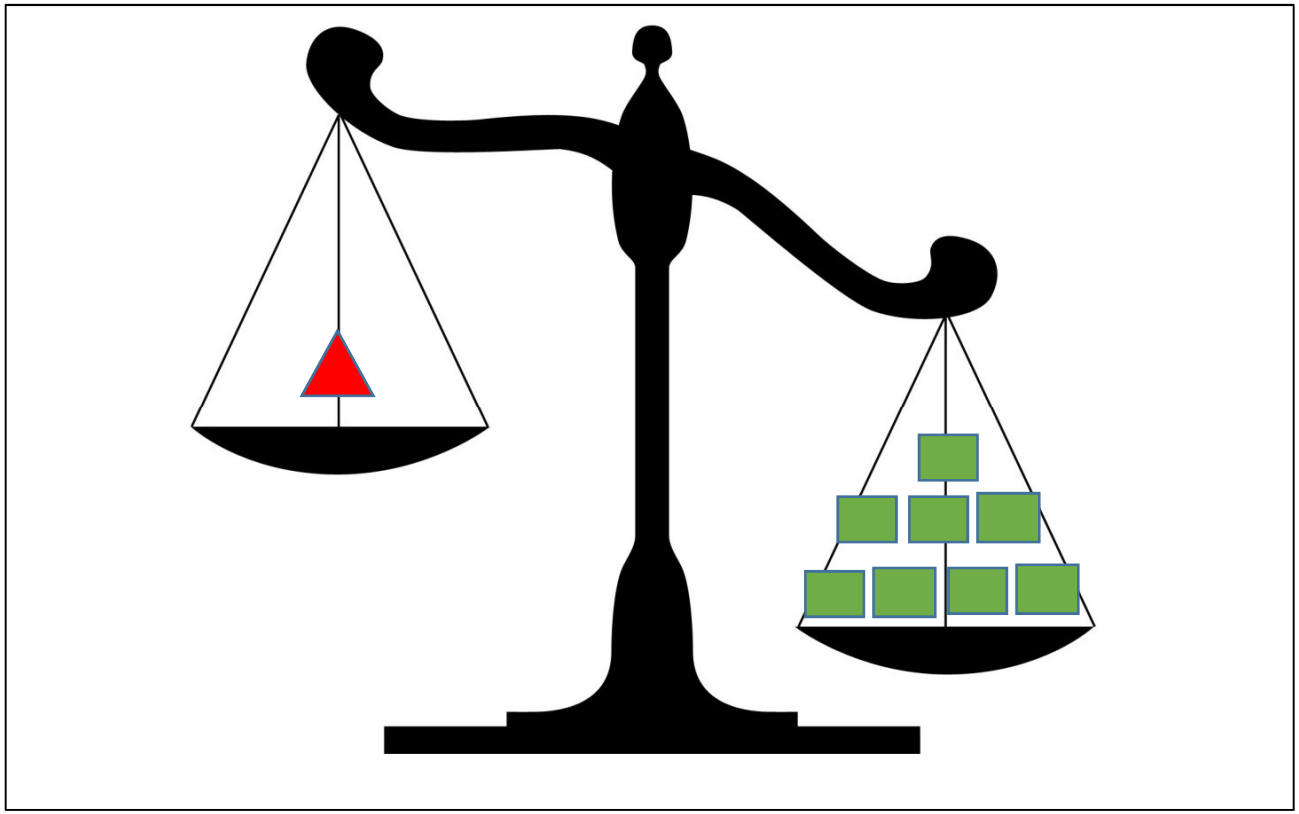


D1 vs. D2

D1-like Dopamine Receptors

D2-like Dopamine Receptors

Pathophysiology: Dopamine Hypothesis



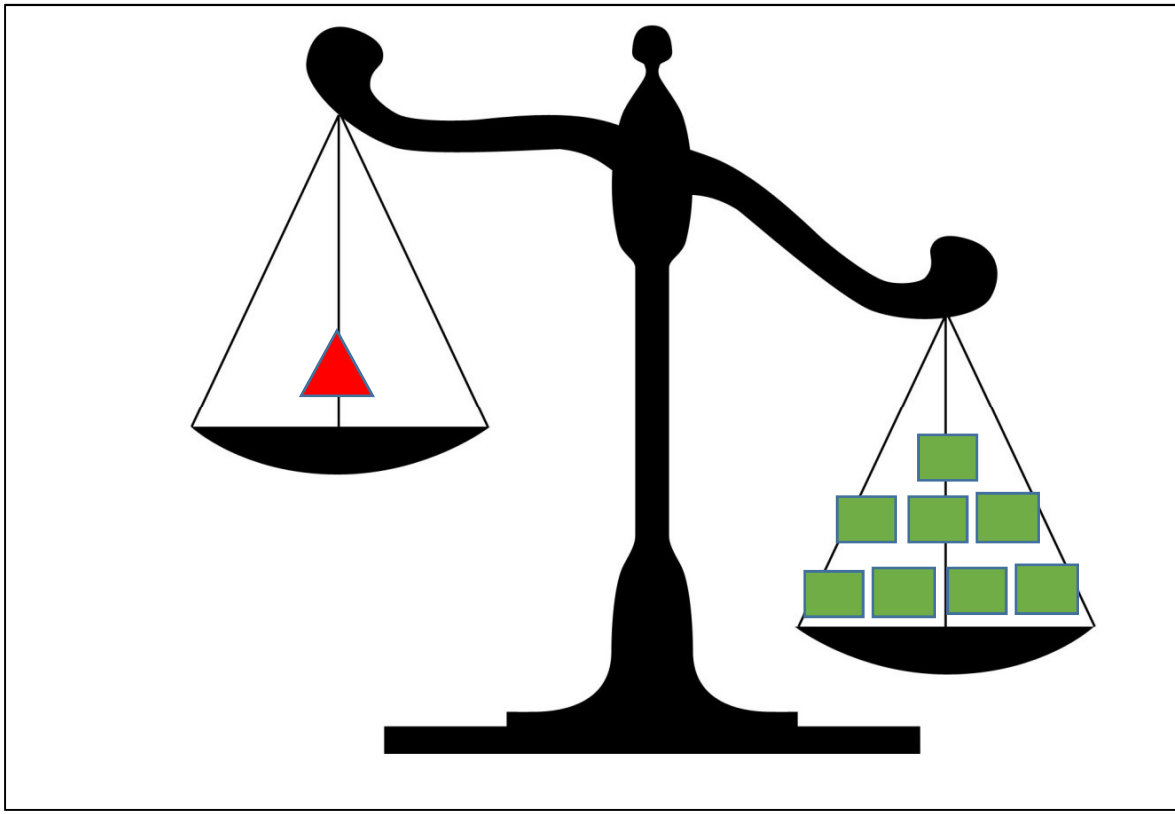
Glutamate (Glu)

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

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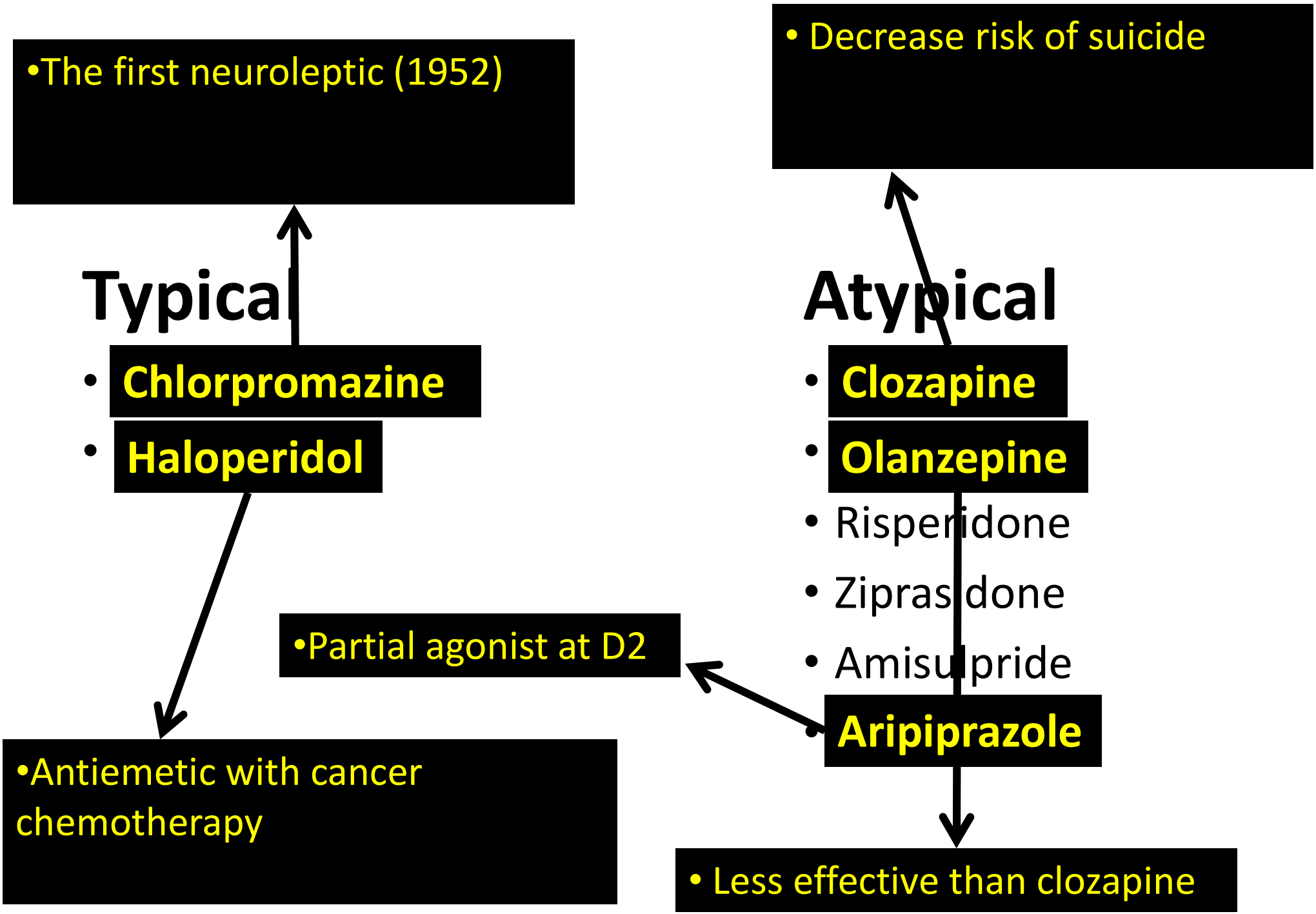
Typical

Atypical

Antipsychotic Drugs

	Typical (First Generation)	Atypical (Second Generation)
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
•Antiemetic with cancer chemotherapy
• Decrease risk of suicide
Atypical
• Clozapine
• Olanzepine
• Risperidone
• Ziprasidone
• Amisulpride
• Aripiprazole
•Partial agonist at D2
• Less effective than clozapine

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. Olanzepine
B. Haloperidol
C. Clozapine
D. Ziprazidone
E. All of the above

Question 3

- **The name of the actor for the main character in the movie beautiful mind is:**

A. John Nash
B. Sylvester Stallone
C. Bruce Willis
D. Thaeir Ghazo
E. Russell Crowe

Question 4

- **Dopamine (D1) receptors are:**

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

Question 5

- **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!