Antipsychotic drugs

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The most common form of psychosis ➔ in which patients exhibit gross disturbances in their comprehension of reality ➔ hallmarks are false perceptions (hallucinations) and false beliefs (delusions)

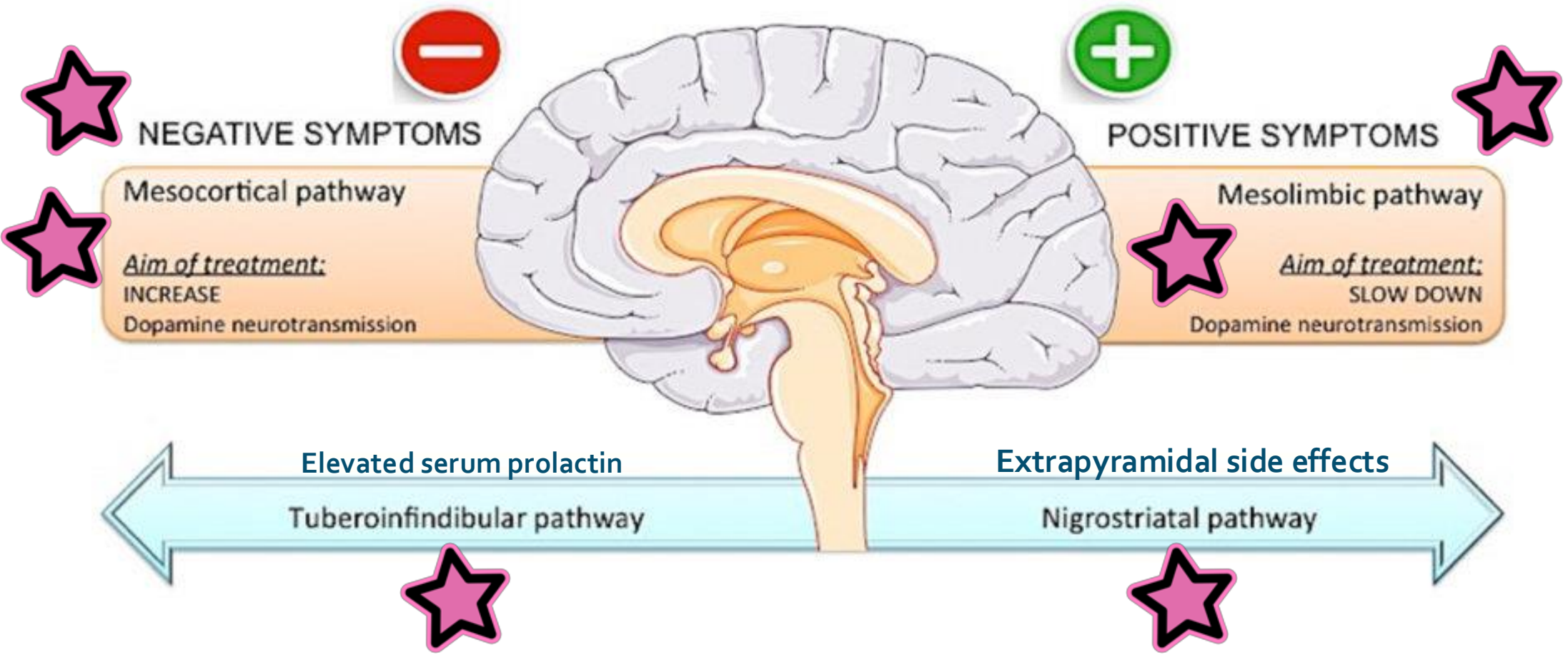
Schizophrenia

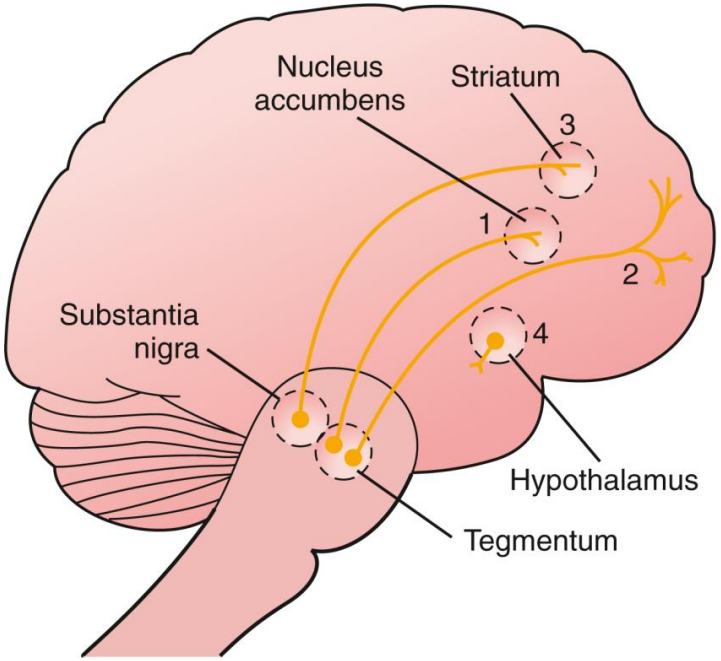
- Result from excessive neuronal activity in mesolimbic pathway.
- Are usually the primary manifestations of acute psychotic episodes.

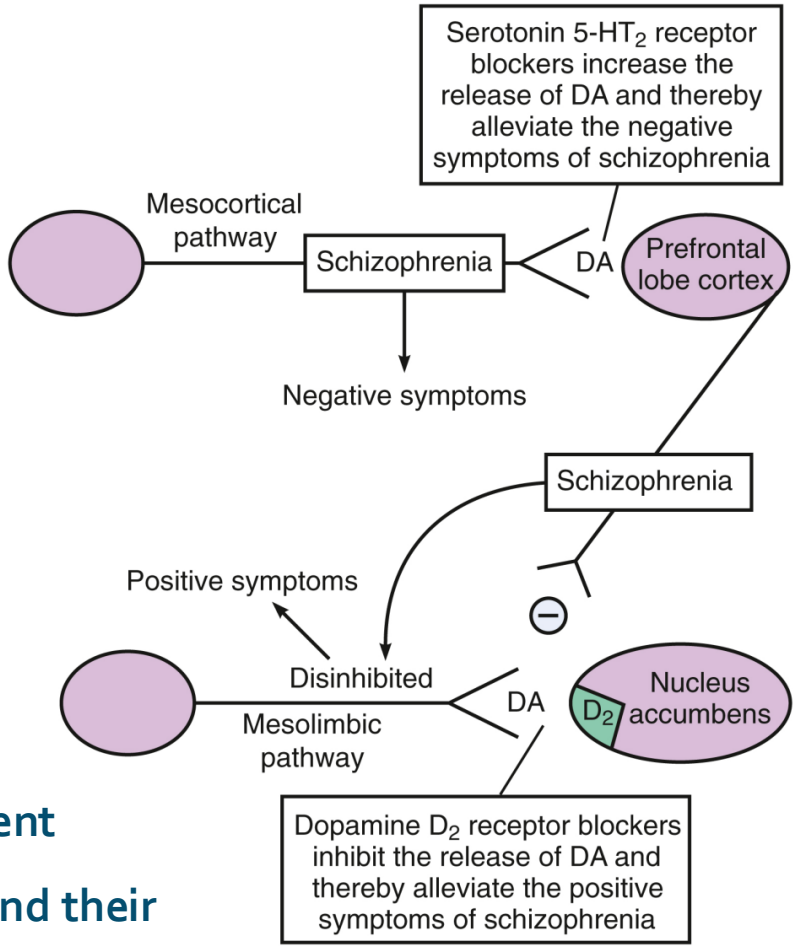
Positive Symptoms	Negative Symptoms
Agitation	Apathy
Delusions	Affective flattening
Disorganized speech	Lack of motivation
Disorganized thinking	Lack of pleasure (anhedonia)
Hallucinations	Poverty of speech
Insomnia	Social isolation

- Result from insufficient activity in mesocortical pathway.
- Generally, more difficult to treat
- Often persist after positive symptoms resolve
- Associated with a poor prognosis.

Dopamine hypothesis







Observations that support the dopamine hypothesis ➔

1. **Most antipsychotic drugs are dopamine D2R blockers ➔ excellent correlation exists between the clinical potency of these drugs and their ability to block D2R**
2. **Drugs that increase dopamine (amantadine, amphetamines and cocaine) ➔ induce psychotic behavior.**

Antipsychotic drugs

Neuroleptic drugs

Mechanism of action

The therapeutic effects of antipsychotic drugs result from ➔ a competitive blockade of dopamine receptors (post synaptic) and serotonin (presynaptic) receptors

1. Typical antipsychotic drugs ➔ have an equal or greater affinity for D2R than for 5-HT2R.
   - An excellent correlation exists between the clinical potency of typical antipsychotics and their affinity for D2R.
   - Blockade of D2R in mesolimbic pathways ➔ alleviate the positive symptoms of schizophrenia
   - Blockade of D2R in the basal ganglia ➔ responsible for the parkinsonian and other EPS side effects.

2. Atypical antipsychotic drugs ➔ have a greater affinity for 5-HT2R than for D2R
   - Blockade of 5-HT2R in mesocortical pathways ➔ increase dopamine in this pathway ➔ effective in reducing the negative symptoms

Classification

Typical

FGAs are D2 antagonists

- They lower neurotransmission in the 4 dopamine pathways.
- They can also block H1, M1 and α1 receptors.

Atypical

SGAs are $5HT_{2A}$ Antagonists

Clozapine was the first SGA.

Very high affinity for $5\text{-}HT_{2A}$

Lower D_2 affinity than haloperidol

TYPICAL ANTIPSYCHOTICS

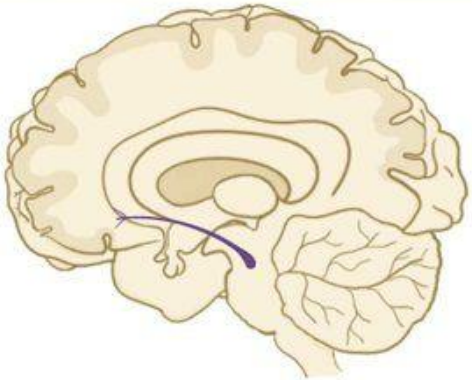
HIGH POTENCY

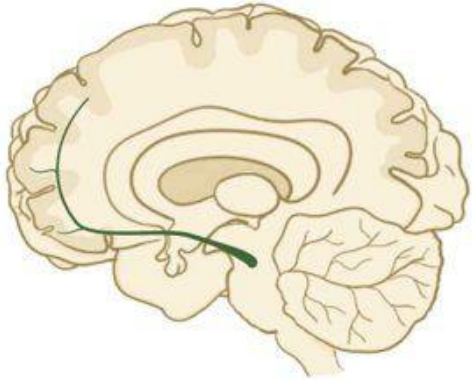
- ~ HALOPERIDOL
- ~ TRIFLUOPERAZINE
- ~ FLUPHENAZINE

LOW POTENCY

- ~ THIORIDAZINE
- ~ CHLORPROMAZINE
- ~ THIOTHIXENE

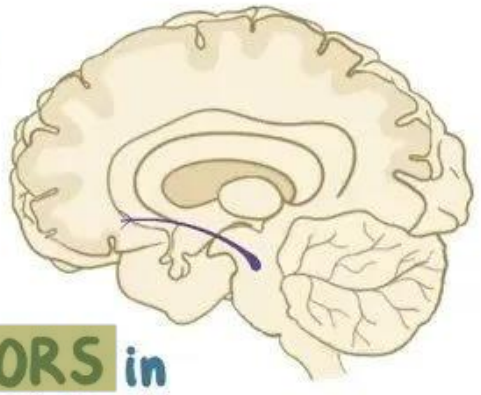
* BLOCK DOPAMINE D2 RECEPTORS in MESOLIMBIC
  - → ALLEVIATE POSITIVE SYMPTOMS



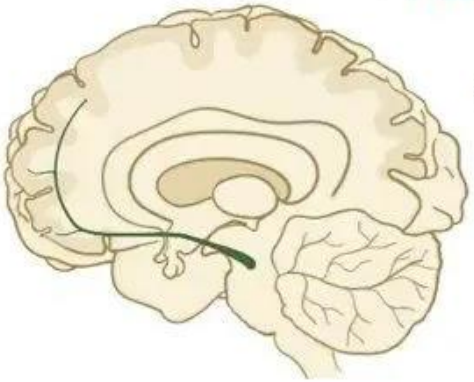


* BLOCK DOPAMINE RECEPTORS in MESOCORTICAL

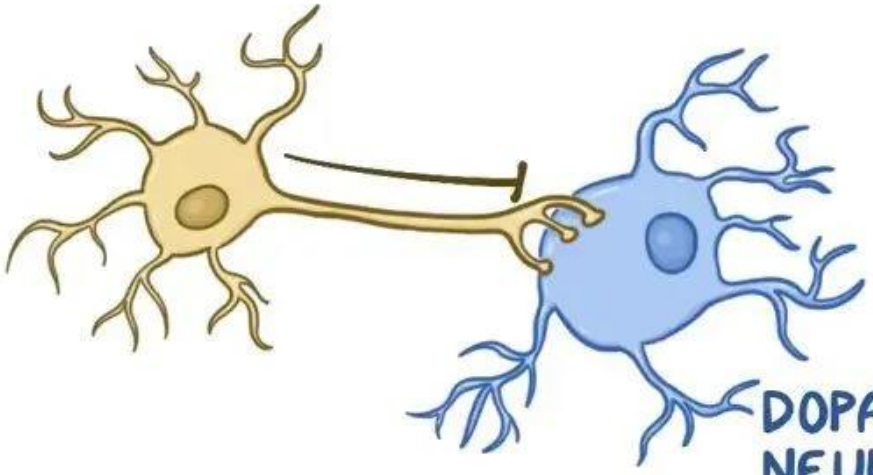
ATYPICAL ANTIPSYCHOTICS



* BLOCK DOPAMINE D_2 RECEPTORS in MESOLIMBIC
  - ↳ ALLEVIATE POSITIVE SYMPTOMS



* BLOCK SEROTONIN 5-HT_{2A} RECEPTORS in MESOCORTICAL
  - ALLEVIATE NEGATIVE SYMPTONS



Pharmacological effects

The therapeutic effects of antipsychotic drugs usually require ~ 6 weeks to fully develop ➔ mechanism is not fully understood

Antipsychotic drugs produce three time-dependent changes in dopamine neurotransmission.

1. When first administered ➔ they increase in dopamine synthesis and release ➔ probably a compensatory response to the acute blockade of postsynaptic D2R.

2. Over time, continued D2R blockade leads to reduced dopamine release ➔ "depolarization blockade".
   - Reduced dopamine release from mesolimbic and nigrostriatal neurons ➔ responsible for improvements in the positive symptoms of schizophrenia while causing EPS side effects.

3. Finally, the reduction in dopamine release caused by depolarization blockade leads to D2R up-regulation and supersensitivity ➔ development of a delayed special type of EPS called tardive dyskinesia

Differentiate among the classes of antipsychotics drugs

	High-Potency Typical Agents	Low-Potency Typical Agents	Atypical Agents *
Prototype drug	Haloperidol	Chlorpromazine	Cariprazine, risperidone, olanzapine, aripiprazole, paliperidone, quetiapine, ziprasidone clozapine
EPS side effects	High incidence	Low incidence	Low incidence
ANS side effects †	Low incidence	High incidence	Medium incidence
Positive symptoms	Works well	Works well	Works well
Negative symptoms	Works poorly	Works poorly	Works fairly well

Side effects ➔ typical antipsychotics

1. Autonomic nervous system ➔ low-potency antipsychotics
   - Block muscarinic R ➔ blurred vision, dry mouth, constipation, and urinary retention.
   - Block α1 R ➔ dizziness, orthostatic hypotension, and reflex tachycardia
   - Block brain H 1R ➔ drowsiness and weight gain.

2. Blockade of D2R in the nigrostriatal pathway ➔ extra pyramidal symptoms (EPS) ➔ the most disturbing ➔ including akathisia (motor restlessness), pseudoparkinsonism, and dystonias ➔ high-potency antipsychotics

3. Blockade of D2R in the tuberoinfundibular pathway ➔ ↑ serum prolactin ➔ gynecomastia in men and menstrual irregularities in women

4. Chlorpromazine ➔ hepatotoxicity (jaundice)

5. Thioridazine ➔ pigment retinopathy and cardiac toxicity.

Side effects ➔ typical antipsychotics

6. Neuroleptic malignant syndrome ➔ a rare, potentially fatal, idiosyncratic side effect

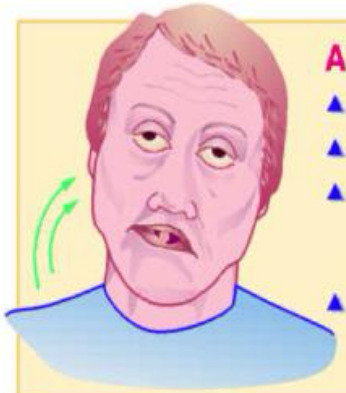
   ➔ linked to high antipsychotic doses.

- It presents with a fever, muscle rigidity, sweating, confusion, and cardiovascular collapse.
- It is associated with elevated creatinine kinase (CK).
- It is associated with a high mortality rate ➔ needs emergent treatment

1. Stop antipsychotic drug.
2. Start DA receptor agonist bromocriptine and the skeletal muscle relaxant dantrolene

Extra pyramidal symptoms (EPS)

Pseudoparkinsonism
- Stooped posture
- Shuffling gait
- Rigidity
- Bradykinesia
- Tremors at rest
- Pill-rolling motion of the hand



Acute dystonia
- Facial grimacing
- Involuntary upward eye movement
- Muscle spasms of the tongue, face, neck and back (back muscle spasms cause trunk to arch forward)
- Laryngeal spasms

Akathisia
- Restless
- Trouble standing still
- Paces the floor
- Feet in constant motion, rocking back and forth

Tardive dyskinesia
- Protrusion and rolling of the tongue
- Sucking and smacking movements of the lips
- Chewing motion
- Facial dyskinesia
- Involuntary movements of the body and extremities

- **Delayed** ➔ develops after months - years of treatment
- Results from **supersensitivity to dopamine** after long-term D2R blockers
- Can be **irreversible**
- Not easily managed ➔ use drug in the **lowest doses** for the **shortest period**

DYSTONIA AKATHISIA AKINESIA TARDIVE DYSKINESIA

Acute Dystonia

Muscle

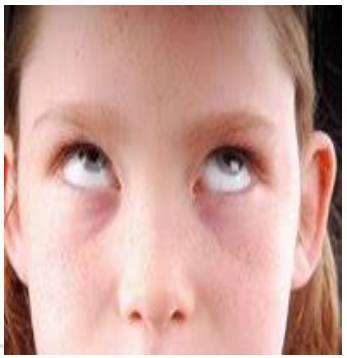
4 Hours

Torticollis

Oculogyric Crisis

Treatment:

Benzotropine



Akathisia

Rustle

4 Days

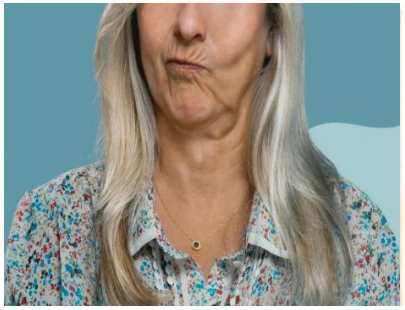
*Ants in the pants

* Tx: Benzo, or B-Blockers

*Swish to New medication

Tardive Dyskinesia

Could be Irreversible



Akinesia Pill Rolling

Hustle

4 Weeks

Bradykineseia

*Decreased facial Expression

*Cogwheel Rigidity

Differential

*Catatonic Rigidity

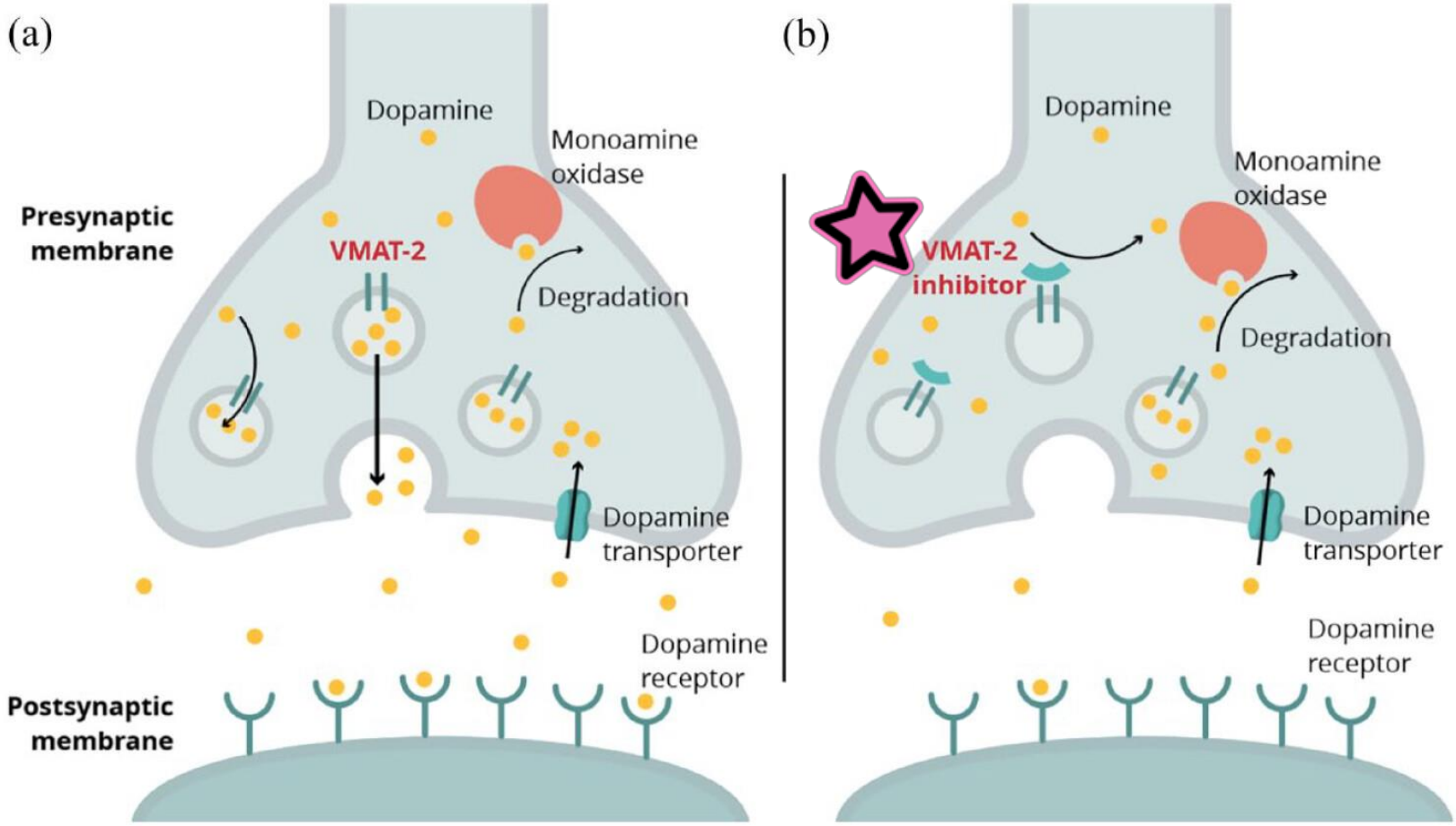
*Withdrawal

Treatment of EPS

- **Acute** extrapyramidal effects (akathisia, pseudoparkinsonism, and dystonia) ➔
  1. **Lower** the antipsychotic **dose**
  2. Change to an **atypical** antipsychotic
  3. Administer a drug to counteract these effects ➔ **benztropine** (an antimuscarinic drug) and/or **amantadine** (increases dopamine release in the basal ganglia)

- **Tardive dyskinesia** ➔ not easily managed
  1. **Lower** the antipsychotic **dose**
  2. **Valbenazine** ➔ approved for the treatment of tardive dyskinesia ➔ **vesicular monoamine transporter type 2 inhibitors** ➔ act centrally to deplete DA storage in presynaptic vesicles.

Valbenazine



Side effects ➔ atypical antipsychotics

Side Effect	Associated Atypical Antipsychotic(s)
Agranulocytosis	Clozapine
Increased prolactin	Risperidone
Weight gain	Olanzapine, quetiapine, clozapine
Extrapyramidal symptoms (EPS)	Paliperidone, aripiprazole
QT prolongation	Ziprasidone, paliperidone, risperidone
Sedation	Olanzapine, quetiapine, clozapine
Orthostatic hypotension	Olanzapine, quetiapine, clozapine
Dry mouth	Olanzapine, quetiapine
Constipation	Clozapine, aripiprazole

White blood cells must be weekly monitored

Less compared to typical

Individual differences ➔ Atypical antipsychotics

1. Clozapine

- Its therapeutic effects result from ➔ blockade of 5-HT2 Rs and D4 Rs ➔ Greater activity against the negative symptoms + significantly fewer EPS
- Block H1, muscarinic, and α1 R ➔ significant sedation and autonomic side effects.
- Associated with a potentially fatal agranulocytosis ➔ mostly during the first-year after initiation ➔ FDA requires weekly monitoring of leukocyte counts during the first 6 months of therapy ➔ then biweekly

2. Olanzapine ➔ like clozapine, but

- Causes fewer autonomic side effects
- Has not been reported to cause agranulocytosis.

Individual differences ➔ Atypical antipsychotics

3. **Risperidone** ➔ like olanzapine, but
   - Cause a higher incidence of EPS.
   - Elevates levels of serum prolactin.
   - lengthens the QT interval ➔ predispose patients to cardiac dysrhythmias, including torsade de pointes

4. **Aripiprazole** ➔ a partial agonist at D2R and 5-HT1 R but a 5-HT2 R antagonist

Treatment Considerations

- Atypical antipsychotic drugs (except clozapine) ➔ 1st choice for the treatment of schizophrenia
- In comparison with the typical drugs ➔ they produce a lower incidence of EPS and appear to be more effective against the negative symptoms.
- Patients exhibit some improvement of positive symptoms during the first 2 weeks of therapy ➔ the maximal response generally requires 6 weeks or longer ➔ then it is possible to reduce the dosage (maintenance therapy).

Treatment Considerations

- Antipsychotic drugs ➔ is usually continued for at least 12 months after the remission of acute psychotic symptoms ➔ then either a low-dose regimen or gradual withdrawal of the drug is considered ➔ to reduce the risk of developing tardive dyskinesia.
- Antipsychotic drugs should be tapered slowly before discontinuation ➔ abrupt discontinuation can cause withdrawal symptoms ➔ insomnia, nightmares, restlessness, nausea, vomiting, diarrhea, salivation, and sweating.