Prepared by M.Sc: Anwer Mahmood

Psychoses

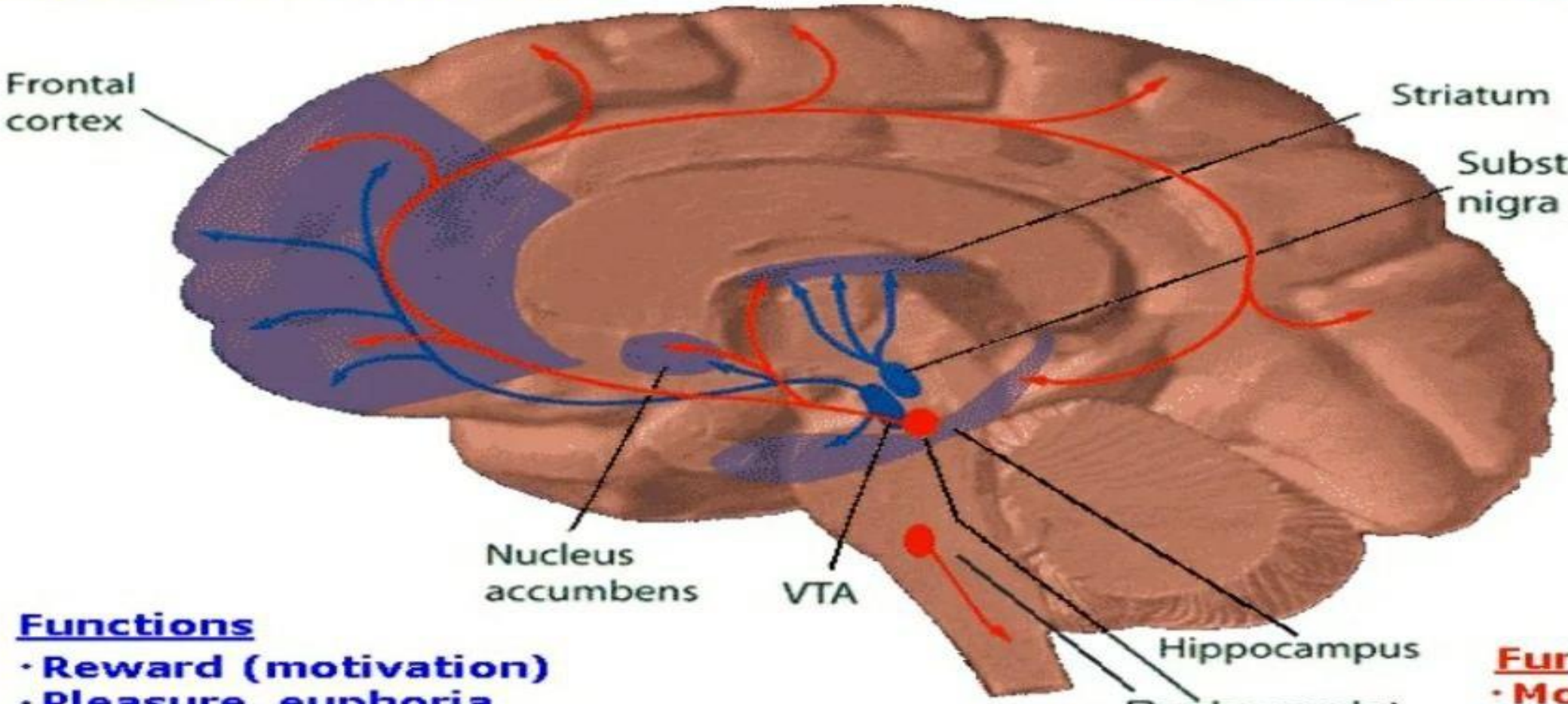
❖**Psychoses** are disorders in which patients' exhibit gross disturbances in their comprehension of reality, as evidenced by false perceptions (**hallucinations**) and false beliefs (**delusions**)

❖The most important types of psychosis are:

1. Schizophrenia
2. Affective disorders (e.g. depression, mania)
3. Organic psychoses (mental disturbances caused by head injury, alcoholism, Alzheimer disease)
4. Toxic psychosis (drug-induced) e.g. amphetamine, L-dopa, Phencyclidine, Cocaine

Dopamine Pathways

Serotonin Pathways



Functions

- Reward (motivation)
- Pleasure, euphoria
- Motor function (fine tuning)
- Compulsion
- Perseveration

Functions

- Mood
- Memory processing
- Sleep
- Cognition

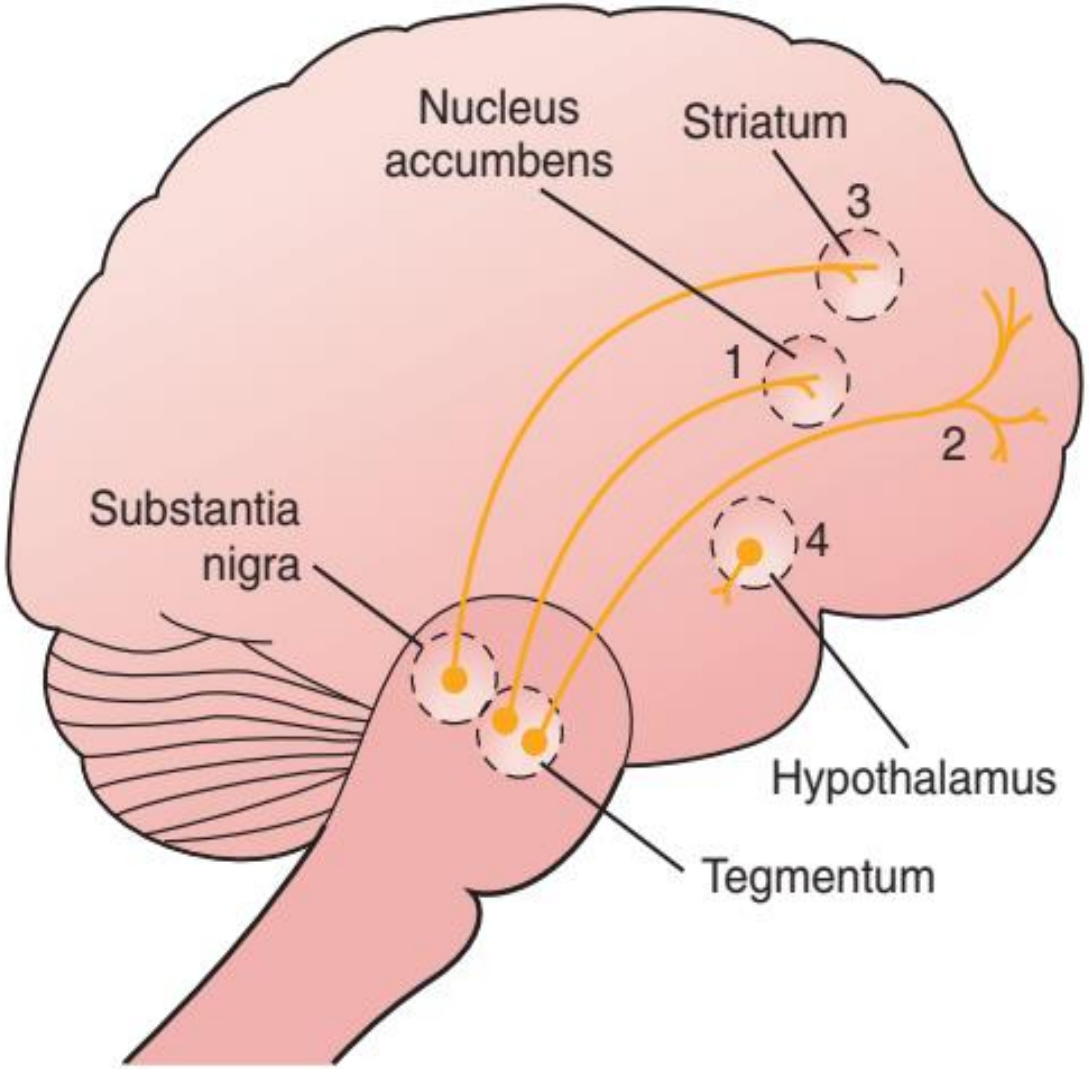
Schizophrenia

- **Schizophrenia** is a type of **chronic** psychosis
- Schizophrenia, the **most common form** of psychosis, affects about 1% of the world's population.
- Its hallmarks are delusions, hallucinations (often in the form of voices), disorganized thinking, and emotional abnormalities.
- The onset of illness is often during late **adolescence** or early **adulthood**.

POSTULATED NEURONAL DYSFUNCTION IN SCHIZOPHRENIA

As shown in the accompanying figure, numerous dopamine pathways are found in the brain.

1. **Mesolimbic pathway.** Dopamine travels from the midbrain tegmental area to the nucleus accumbens. Increased activity in this pathway may cause delusions, hallucinations, and other so-called *positive symptoms* of schizophrenia.
2. **Mesocortical pathways.** There are several mesocortical pathways. Decreased activity in the pathway that goes from the midbrain to the prefrontal lobe cortex can cause apathy, withdrawal, lack of motivation and pleasure, and other so-called *negative symptoms* of schizophrenia. Mesocortical dysfunction also disinhibits the mesolimbic pathway.
3. **Nigrostriatal pathway.** The pathway from the substantia nigra to the striatum is involved in the coordination of body movements. Inhibition of this pathway causes the extrapyramidal side effects of antipsychotic drugs.
4. **Tuberoinfundibular pathway.** The pathway from the hypothalamus to the pituitary inhibits the release of



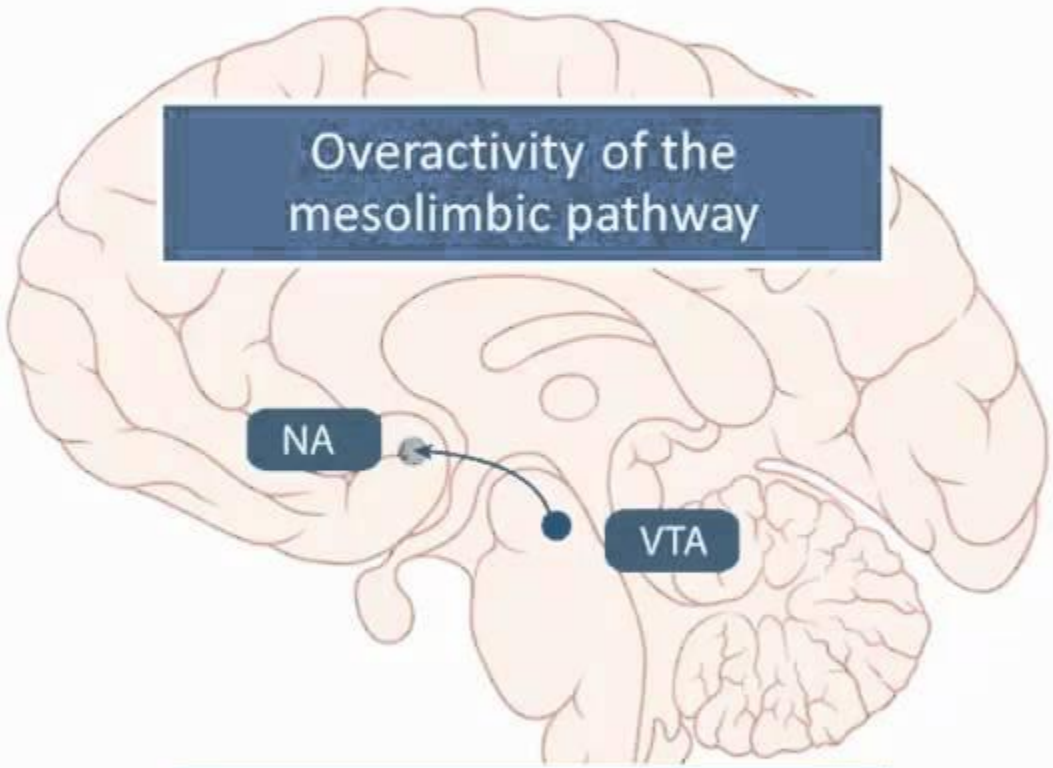
symptoms of schizophrenia

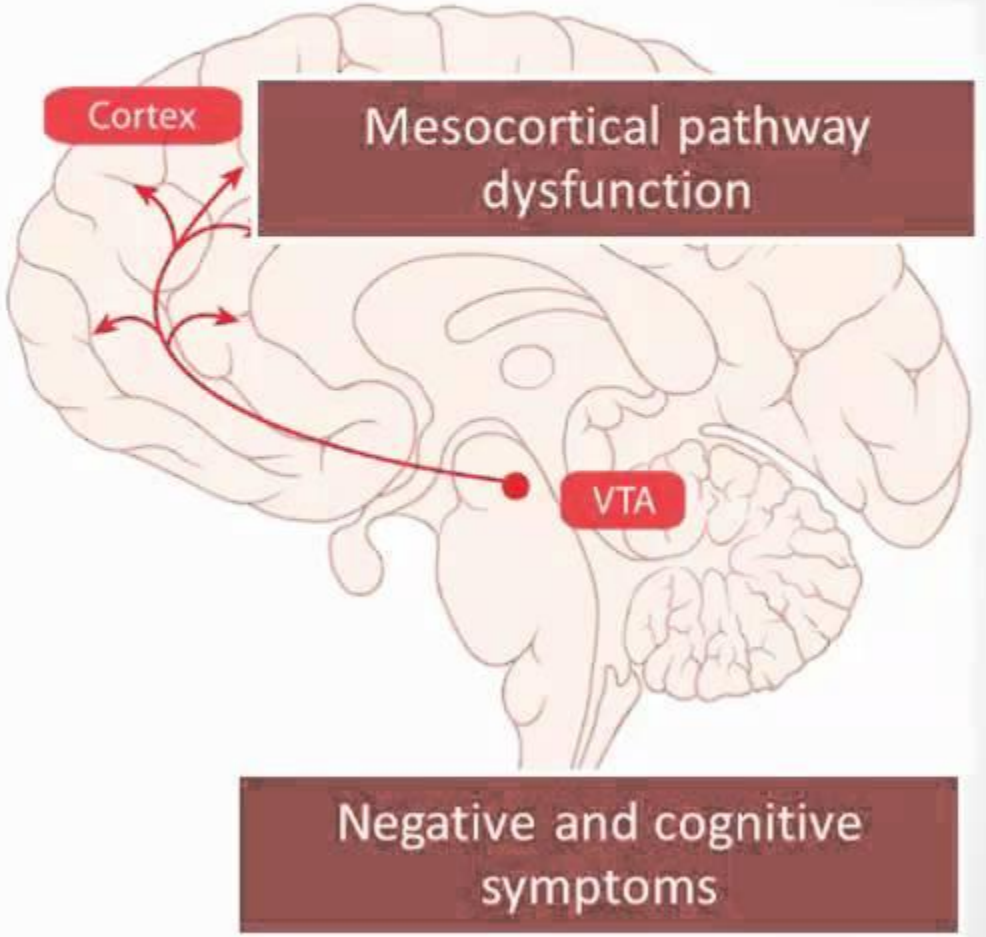
- The symptoms divided into two groups.
- The **positive symptoms**, which include delusions and hallucinations, probably result from excessive neuronal activity in mesolimbic neuronal pathways.
- These symptoms are usually the primary manifestations of acute psychotic episodes.
- The **negative symptoms**, which include apathy, withdrawal, and lack of motivation and pleasure, probably result from insufficient activity in mesocortical neuronal pathways.
- The **negative symptoms** generally are more **difficult** to treat, often persist after positive symptoms resolve, and are associated with a **poor prognosis**

POSITIVE SYMPTOMS
Agitation
Delusions
Disorganized speech
Disorganized thinking
Hallucinations
Insomnia

NEGATIVE SYMPTOMS
Apathy (avolition)
Affective flattening
Lack of motivation
Lack of pleasure (anhedonia)
Poverty of speech (alogia)
Social isolation

Dopamine Pathways Relevant to Schizophrenia Symptoms





Hypothesis of schizophrenia

- **Dopamine hypothesis:**
- Evidence support dopamine hypothesis:
- First, many **antipsychotic drugs block brain D** receptors (especially D2 receptors).
- Second, **dopamine agonist** drugs (e.g. amphetamine, levodopa) exacerbate schizophrenia.
- Third, an **increased density of dopamine** receptors has been detected in certain brain regions of untreated schizophrenics.
- Successful treatment of schizophrenia changes **HVA** in CSF, plasma, urine of patients (homovanillic acid -a Dopamine metabolite decreased as the patient improved)

Evidence against Dopamine Hypothesis

- Antipsychotic drugs are only **partly effective** in most patients
- **Phencyclidine**, an NMDA receptor antagonist, produces more schizophrenia-like symptoms in non-schizophrenic subjects than Dopamine agonists.
- **Atypical antipsychotics** have low affinity for D2 receptors

dopaminergic systems in CNS

Site	Dopamine	Dopamine Antagonists
1- Limbic system, Frontal cortex	1- Euphoria then Psychosis	1- Anti-Psychotic.
2- Basal Ganglia.	2- Anti-Parkinsonian.	2- Parkinsonism.
3- Hypothalamus.	3- ⇧ Temperature ⇩ Appetite ⇩ Prolactin	3- ⇩ Temperature → Hypothermia ⇧ Appetite ⇧ Prolactin
4- C. T. Z.	4- Nausea & Vomiting	4- Anti-emetic EXCEPT in motion sickness

❖D2 over-activity in mesolimbic pathway → +ve symptoms (typical antipsychotics are effective because they are strongly bind to D2)

Antipsychotics=neuroleptics=major tranquilizer

❖**Classification:**

- **Older typical antipsychotic also called conventional, or traditional antipsychotics**: include

1. **Phenothiazines** (eg, chlorpromazine, thioridazine, fluphenazine),
2. **Thioxanthenes** (eg, thiothixene),
3. **Butyrophenones** (eg, haloperidol, droperidol).

- **Newer atypical antipsychotic**: including clozapine, olanzapine, risperidone, quetiapine, ziprasidone, and aripiprazole.
- Used first-line therapy for schizophrenia to minimize the risk of debilitating EPS associated with 1st G

MECHANISM OF ACTION OF ANTIPSYCHOTICS

- **Dopamine antagonism**: All of the first-generation and most of the second-generation antipsychotic drugs block **D2** dopamine receptors in the brain(in the **limbic** system and **mesocortical** areas) and the periphery.
- **Serotonin receptor–blocking activity**: Most of the second-generation block of (5-HT) receptors, particularly **5-HT 2A (inhibitory autoregulation)** receptors in **mesolimbic** system.

Actions

1. **Antipsychotic effects**: All antipsychotic ↓ positive" symptoms by × D2R in the **mesolimbic system**. Negative symptoms not response to 1st G. many 2nd G can treat negative symptoms to some extent.
2. **Extrapyramidal effects**: **Dystonias** (sustained contraction of muscles leading to twisting, distorted postures), **Parkinson-like symptoms**, **akathisia** (motor restlessness), and **tardive dyskinesia** (involuntary movements, usually of the tongue, lips, neck, trunk, and limbs) can occur with both acute and chronic treatment. Blockade of dopamine receptors in the **nigrostriatal pathway** probably causes these unwanted movement symptoms. **The 2nd G exhibit a lower incidence of EPS.**

Actions

3. **Antiemetic effects**: With the exception of **aripiprazole**, most of the antipsychotic drugs have antiemetic effects that are mediated by **blocking D2 receptors** of the **chemoreceptor trigger zone** of the medulla.

4. **Anticholinergic effects**: Some of the antipsychotics, particularly thioridazine, chlorpromazine, clozapine, and olanzapine, produce anticholinergic effects. The anticholinergic effects may actually assist in reducing the risk of EPS with these agents.

Actions

5. **Other effects**:

- **Blockade of α-adrenergic** receptors causes orthostatic hypotension and light-headedness failure of ejaculation .
- The antipsychotics also **alter temperature-regulating mechanisms** and can produce poikilothermia (condition in which body temperature varies with the environment).
- In the pituitary, antipsychotics block D2 receptors, leading to an **increase in prolactin release**.
- **Sedation** occurs with those drugs that are potent antagonists of the H1-histamine receptor, including chlorpromazine, olanzapine, quetiapine, and clozapine.
- **Sexual dysfunction** may also occur with the antipsychotic.

Therapeutic uses

❖Treatment of schizophrenia

1. ↓ **positive symptoms** – Hyperactivity – Bizarre ideation – Hallucinations and delusions. **Beneficial effects may take several weeks** to develop. Individual patients may respond best to specific drugs. Typical drugs are still in used due to low cost.
2. **Negative symptoms** – Typical drugs do not have much effect. Newer atypical drugs improve some like emotional blunting, Social withdrawal.

❖Other psychiatric and neurologic uses:

➢Chlorpromazine used for → intractable hiccups.

➢Pimozide used for → motor and phonic tics of Tourette disorder.

Therapeutic uses

- Risperidone and haloperidol used for → disruptive behavior and irritability secondary to **autism**.
- Many antipsychotic used for → **manic** and mixed symptoms associated with **bipolar disorder**.
- Lurasidone and quetiapine are indicated for the treatment of **bipolar depression**.
- Some antipsychotics (aripiprazole and quetiapine) are used as adjunctive agents with antidepressants for treatment **of refractory depression**.

❖Nonpsychiatric indications

- **Antiemetic action**: due to D receptor blocking central and peripheral. Most typical antipsychotics with **exception of thioridazine** has no antiemetic action
- **Antipruritics**: H 1 receptor blockade basis for use-promethazine
- **Intractable Hiccup** -chlorpromazine

Pharmacokinetic

- **Absorption** is variable is unaffected by food (except for **ziprasidone** and **paliperidone**, the absorption of which is **increased** with food).
- Have a **large volume** of distribution and enter CNS.
- They are **metabolized in the liver**, some metabolites are active and have been developed as pharmacological agents themselves (for example, paliperidone is the active metabolite of risperidone).
- **Long-acting injectable** (LAI) formulations with duration of action of up to 2 to 4 weeks.
- Antipsychotics are almost completely metabolized and thus, very little is eliminated unchanged.
- Elimination half-lives are 10-24 hrs.

Adverse effects

❖**Extrapyramidal effects**: This side effect is **time** and **dose** dependent

➢**Dystonias** occurring within → a few hours to days of treatment, followed by

➢**Akathisias** occurring within days to weeks.

➢**Parkinson like symptoms** of bradykinesia, rigidity, and tremor usually occur within weeks to months of initiating treatment.

➢This side effect is treated by administration of an **anticholinergic drug**, such as benztropine.so thioridazine exhibit strong anticholinergic activity → show fewer EPS, while haloperidol and fluphenazine has low anticholinergic activity → ↑incidence of EPS due to blocking D transmission.

➢**Akathisia** may respond better to β blockers (for example, propranolol) or benzodiazepines, rather than anticholinergic medications.

Adverse effects

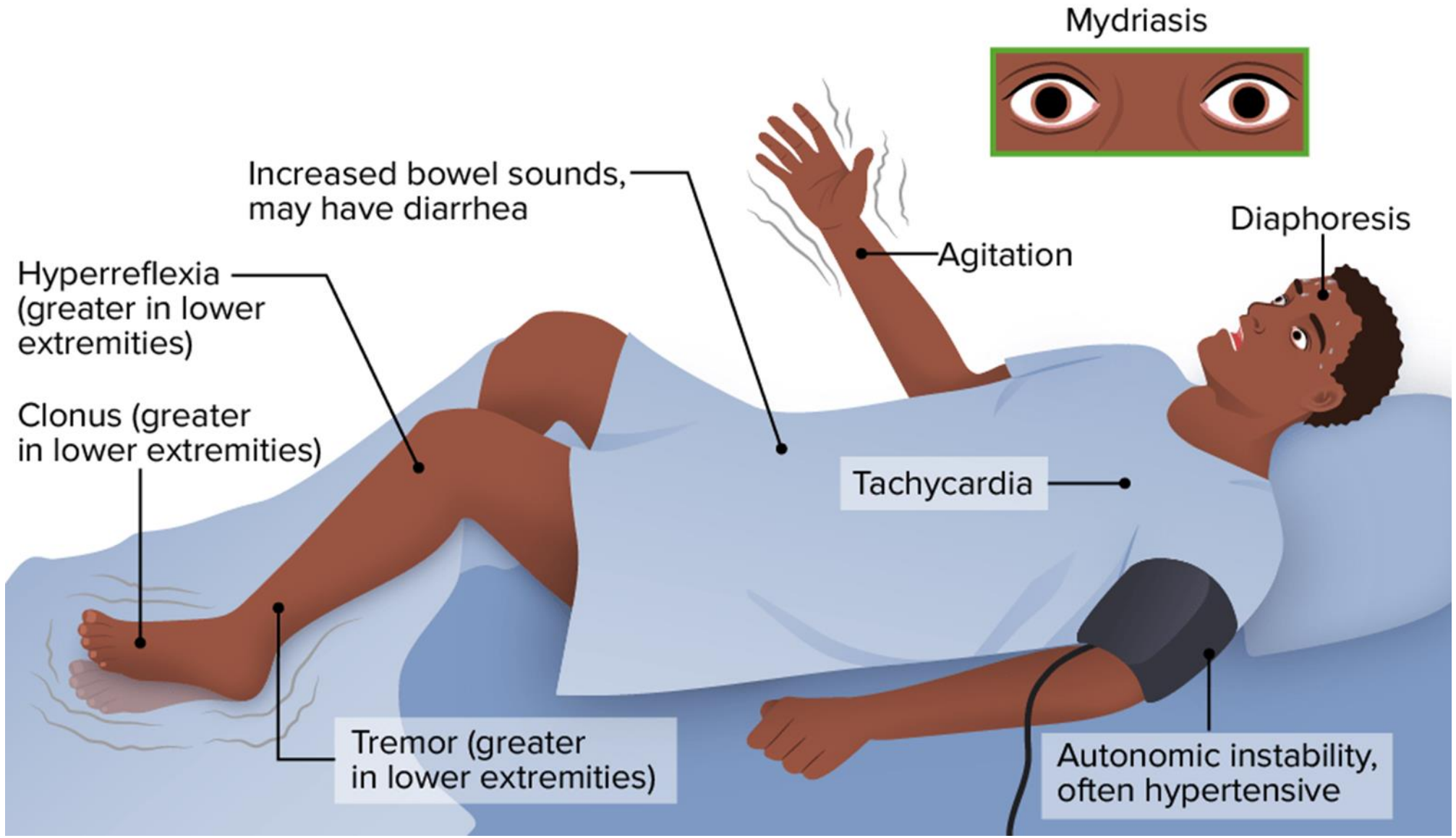
Tardive dyskinesia, which can be **irreversible**, may occur after months or years of treatment.

Tardive dyskinesia: Long-term use → cause this motor disorder. Patients display involuntary movements, including bilateral and facial jaw movements and "fly-catching" motions of the tongue. It's treated by holiday from antipsychotics → symptoms to diminish or disappear within a few months, in many individuals, tardive dyskinesia is irreversible and persists after discontinuation of therapy. Tardive dyskinesia is postulated to result from ↑ no of DR that are synthesized as a compensatory response to long-term DR blockage so ↑ neuron sensitivity to D so the dopaminergic input overpower the cholinergic input→ excess movement. Traditional anti-EPS medications may actually worsen this condition.


St. Thomas' Hospital

Adverse effects

- **Neuroleptic malignant syndrome**: Patients who are particularly **sensitive** to the **extrapyramidal** effects of antipsychotic drugs may develop a malignant hyper thermic syndrome.
- Due to excessively rapid blockade of postsynaptic dopamine receptors
- The symptoms include muscle rigidity, impairment of sweating, hyperpyrexia, and autonomic instability, which may be life threatening.
- Drug treatment involves the prompt use of dantrolene, diazepam, and dopamine agonists.


Mydriasis
Increased bowel sounds, may have diarrhea
Diaphoresis
Agitation
Hyperreflexia (greater in lower extremities)
Clonus (greater in lower extremities)
Tachycardia
Tremor (greater in lower extremities)
Autonomic instability, often hypertensive

Adverse effects

❖**Endocrine and metabolic effects**: *dopamine is the normal inhibitory regulator of prolactin secretion*. D2 receptor blockade in the pituitary cause hyperprolactinemia

1. In female: Galactorrhea ,↓FSH, LH→ amenorrhea
2. In male: hyperprolactinemia → infertility, ↓lipido (↓FSH,LH which effect testicular production of testosterone).impaired ejaculation (esp chlorpromazine)

Elevated prolactin is prominent with **risperidone**.

Significant **weight gain** and **hyperglycemia** due to a diabetogenic action occur with several of the **atypical agents**, especially clozapine and olanzapine.

Aripiprazole and **ziprasidone** have little or no tendency to cause hyperglycemia, hyperprolactinemia, or weight gain.

Adverse effects

❖Other effects:

1. **CNS depression and antihistaminic** effects → Drowsiness, usually during the first few weeks of treatment.
2. Some antipsychotic has potent **antimuscarinic** activity → anticholinergic SE.
3. Others block **α-adrenergic R**, → ↓ BP and orthostatic hypotension.
4. Some drug associated with **mild to significant QT prolongation**. **Thioridazine** has the **highest** risk.
5. **Visual impairment** caused by retinal deposits has occurred with **thioridazine**. Deposit in cornea and lens (**chlorpromazine**)
6. **Clozapine** causes **agranulocytosis** and at high doses has caused **seizures**.

Drug Interactions

- Additive effects with sedatives.
- Additive effects with anticholinergics.
- Additive effects with antihistaminergics.
- Additive effects with α-AR blocking drugs.
- Additive effects with drugs with quinidine-like action (thioridazine).

Typical antipsychotics	*Atypical antipsychotics*
Bind strongly to D2 receptors	Bind with low affinity to D2 Block 5-HT receptors
More Extrapyramidal side effect	Less EPSE
May cause neuroleptic syndrome	Rare
Effective especially for +ve symptoms	Effective for both –ve and +ve symptoms
Associated with less wt gain	Associated with more wt gain
Decrease threshold for seizure	Less effect

Refractory patients

- Approximately **10% to 20%** of patients with schizophrenia have an insufficient response to **all first- and second**-generation antipsychotics.
- For these patients, **clozapine** has shown to be an effective antipsychotic with a minimal risk of EPS.
- Its clinical use is limited to refractory patients because of serious adverse effects.
- Clozapine can produce bone marrow suppression, seizures, and cardiovascular side effects.
- The risk of severe agranulocytosis necessitates frequent monitoring of white blood cell counts

Chlorpromazine

- Chlorpromazine
- **Potent** D2-blockade M, H1 and α blockade
- **Low potency**
- **Significant** sedation and hypotension

Haloperidol and fluphenazine

- Haloperidol, fluphenazine
- Potent D2-blockade M, H1 and α-blockade
- **Potent antipsychotics**
- **Less** sedation and hypotension
- **Weak** anticholinergic
- **Marked** EPS
- Hyperprolactinaemia
- Jaundice rare

Clozapine

- Clozapine Potent 5-HT2 blockade D2- (weak), M, H1 and α-blockade
- **5-HT2C inverse agonists**.
- Sedation and hypotension +++
- Less EPS
- Anticholinergic
- **Minimal effect on prolactin**
- **Agranulocytosis**
- **Precipitate seizures, weight gain**
- **Hypersalivation**
- **Reserve drug for resistant cases**

Olanzapine

- Olanzapine Potent 5-HT2 blockade D2- (weak), M, H1 and α-blockade
- **5-HT2C inverse agonists.**
- Sedation +, hypotension +++
- Less EPS
- **Minimal effect on prolactin**
- **Potent anticholinergic**
- **Precipitates seizures, weight gain**
- Hyperglycaemia

Risperidone

- Risperidone 5-HT2 blockade D2-, M, H1 and α-blockade
- Sedation, hypotension ++
- **Low doses (6 mg/d) less EPS**
- Increases prolactin levels
- **Less likely to cause seizures**

Ziprasidone

- Ziprasidone 5-HT2 , D2-blockade
- Less EPS

Quetiapine

- Quetiapine 5-HT1A, 5-HT2, D2-blockade
- **Sedation +++**
- **QT** prolongation

Aripiprazole

- Aripiprazole 5-HT2 blockade
- **D2 partial agonist**
- Minimal effect on prolactin
- Less weight gain
- Less hyperglycemia

	D_2 Block	D_4 Block	α_1 Block	5-HT_2 Block	M Block	H_1 Block	Special notes
Typical							
1- Most phenothiazines & thioxanthenes	++	-	++	+	+	+	Extrapyramidal dysfunction, tardive dyskinesias and hyperprolactinemia
2- Thioridazine	++	-	++	+	+++	+	
3- Haloperidol	+++	-	+	-	-	-	Extrapyramidal dysfunction (major)
Atypical							
1- Clozapine	-	++	++	++	++	+	Agranulocytosis, DM and weight gain
2- Olanzapine	+	-	+	++	+	+	DM and weight gain
3- Quetiapine	+	-	+	++	+	+	QT prolongation
4- Risperidone	++	-	+	++	+	+	Hyperprolactinemia
5- Ziprasidone	++	-	++	++	-	+	QT prolongation
6- Aripiprazole	+	+	+	++	-	+	


THANK YOU