Mechanism of Action of Antipsychotics

Antipsychotics , also called **neuroleptics** , are a class of psychotropic medications used primarily in the treatment of **psychotic disorders** such as **schizophrenia** , **bipolar disorder** , and **drug-induced psychosis** . They are also used off-label for **agitation** , **delirium** , and **behavioral disturbances in dementia** .

> **High-Yield** : Antipsychotics manage **positive symptoms** (hallucinations, delusions) and some **negative symptoms** (apathy, social withdrawal) of schizophrenia.

Mechanism of Action

Antipsychotics act primarily by **blocking dopamine D2 receptors** in various brain regions. Additional effects on **serotonin (5-HT)** , **acetylcholine (muscarinic)** , **histamine (H1)** , and **adrenergic (?1)** receptors explain their therapeutic effects and side effects.

Dopamine Receptor Subtypes:

- **D1 and D5** : Primarily involved in motor activity and cognitive function.
- **D2, D3, D4** : Implicated in psychosis; **D2** blockade is most strongly correlated with antipsychotic efficacy.

Classification

First-Generation (Typical) Antipsychotics

- **Mechanism** : Potent **D2 receptor antagonists**
- **Primary use** : Positive symptoms of schizophrenia
- **Examples** :
  - **Haloperidol**
  - **Fluphenazine**
  - **Chlorpromazine**
  - **Thioridazine**
- **Side Effects** :
  - **Extrapyramidal symptoms (EPS)** : dystonia, akathisia, parkinsonism, tardive dyskinesia
  - **Hyperprolactinemia**
  - **Neuroleptic Malignant Syndrome (NMS)**
  - Sedation, orthostatic hypotension (?1 blockade)
  - Anticholinergic effects (especially low-potency agents)

> **High-Yield** : Potency ? effectiveness, but **high-potency** agents (e.g., haloperidol) cause **more EPS** , while **low-potency** agents (e.g., chlorpromazine) cause **more anticholinergic** and **sedative** effects.

Second-Generation (Atypical) Antipsychotics

- **Mechanism** : D2 antagonism + 5-HT2A antagonism (dual action)
- **Use** : Positive and **negative symptoms** , mood disorders
- **Examples** :
  - **Risperidone**
  - **Olanzapine**
  - **Clozapine**
  - **Quetiapine**
  - **Aripiprazole** (partial D2 agonist)
  - **Ziprasidone**
- **Advantages** :
  - Lower risk of EPS
  - Better for **negative symptoms**
  - Lower risk of hyperprolactinemia (except risperidone)
- **Major Side Effects** :
  - **Weight gain** , **diabetes mellitus** , **dyslipidemia** (especially with clozapine and olanzapine)
  - **Agranulocytosis** (clozapine)
  - QT prolongation (ziprasidone)
  - Sedation

> **Clozapine** is the **most effective** antipsychotic for **treatment-resistant schizophrenia** , but requires **WBC monitoring** due to risk of agranulocytosis.

Depot (Long-Acting Injectable) Antipsychotics

Depot formulations improve **adherence** and are useful in maintenance therapy after stabilization with oral antipsychotics.

Drug	Duration	Vehicle
Fluphenazine decanoate	7–28 days	Sesame oil
Haloperidol decanoate	Up to 4 weeks	Sesame oil
Risperidone microspheres	2 weeks	Water-based
Paliperidone palmitate	1–3 months	Aqueous suspension
Aripiprazole monohydrate	Monthly	Aqueous suspension

> **Key Point** : Use **IM depot** after initial stabilization with oral meds. The depot helps maintain therapeutic plasma levels and prevent relapse.

Clinical Uses of Antipsychotics

- **Schizophrenia**

- **Schizoaffective disorder**
- **Bipolar mania**
- **Acute psychosis** (including substance-induced)
- **Tourette syndrome**
- **Delirium and agitation**
- **Psychosis in dementia** (cautious use)

Boxed Warning : Antipsychotics in elderly patients with dementia-related psychosis are associated with **increased risk of death** (mostly due to cardiovascular events and infections).

Important Adverse Effects by System

System	Effect
Neurological	EPS, NMS, tardive dyskinesia
Endocrine	Hyperprolactinemia, galactorrhea
Cardiac	QT prolongation (risk of torsades)
Metabolic	Weight gain, diabetes, dyslipidemia
Hematologic	Agranulocytosis (clozapine)
Anticholinergic	Dry mouth, urinary retention, constipation

Extrapyramidal Symptoms (EPS) Timeline

Time	EPS Type	Treatment
Hours–days	Acute dystonia	Benztropine or diphenhydramine
Days–weeks	Akathisia (restlessness)	?-blockers or benzodiazepines
Weeks–months	Parkinsonism	Anticholinergics (benztropine)
Months–years	Tardive dyskinesia	Switch to atypical (e.g., clozapine), consider VMAT2 inhibitors

Neuroleptic Malignant Syndrome (NMS)

- **Life-threatening** reaction
- Features: **Fever, muscle rigidity, autonomic instability, elevated CPK**
- Treatment:
  - Discontinue drug
  - **Dantrolene** or **bromocriptine**
  - Supportive care

Clinical Pearls

- Use **haloperidol or risperidone** for acute agitation (often IM in emergency settings).

- Clozapine is reserved for **treatment-resistant schizophrenia** .
- **Monitor weight, glucose, and lipids** regularly with atypicals.
- Depot antipsychotics improve **compliance** in chronic psychotic disorders.
- For elderly with dementia-related psychosis, **non-pharmacological** interventions are preferred.