Pharmacology II, 4th Stage

Lippincott's Illustrated Reviews, 6th ed.

Unit III: Drugs Affecting the Central Nervous System

11-Antipsychotics

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The antipsychotic drugs

- The antipsychotic drugs (also called neuroleptics or major tranquilizers) are used primarily to treat schizophrenia, and other psychotic and manic states.
- Psychosis is when people lose some contact with reality. This might involve seeing or hearing things that other people cannot see or hear (hallucinations) and believing things that are not actually true (delusions).
- Antipsychotic drugs are not curative and do not eliminate chronic thought disorders, but they often decrease the intensity of hallucinations and delusions and permit the person with schizophrenia to function in a supportive environment.

Terminology: neuroleptics

Neuroleptic: term used for first generation (typical) antipsychotics because of their ability to produce neurolepsis.

Neurolepsis

- Psychomotor slowing
- Emotional quieting
- Affective indifference

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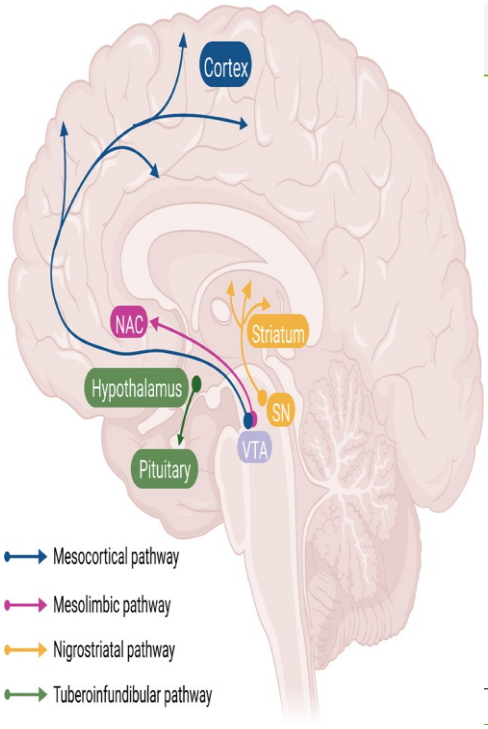
Antipsychotic Drugs

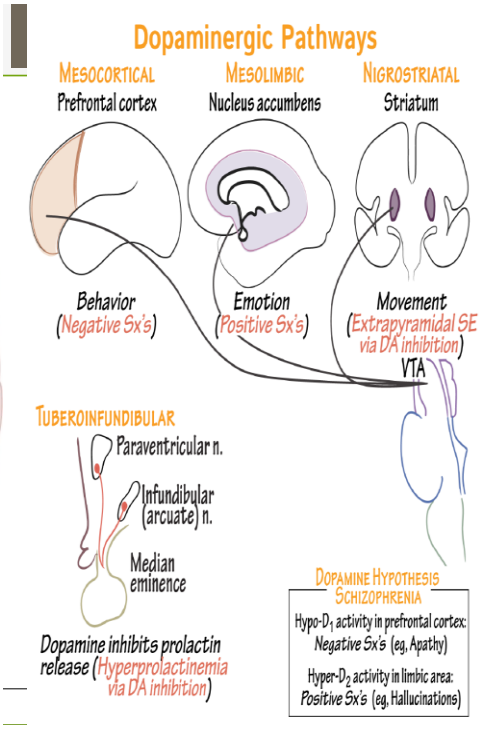
First-Generation (Low Potency)	First-Generation (High Potency)	Second-Generation
Chlorpromazine	Fluphenazine	Aripiprazole
Thioridazine	Haloperidol	Asenapine
	Loxapine	Clozapine
	Pimozide	Iloperidone
	Prochlorperazine	Lurasidone
	Thiothixene	Olanzapine
	Trifluoperazine	Quetiapine
		Paliperidone
		Risperidone
		Ziprasidone

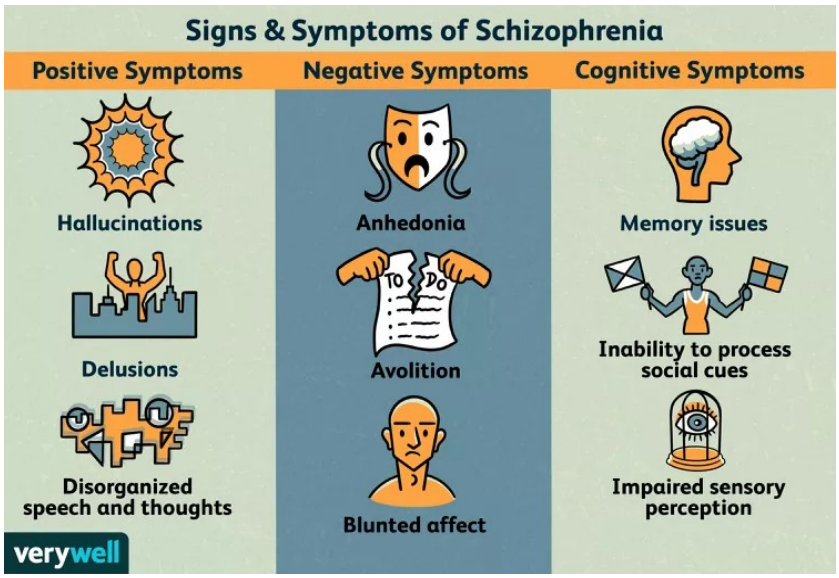
Schizophrenia

- Schizophrenia is a type of chronic psychosis characterized by delusions, hallucinations (often in the form of voices), and thinking or speech disturbances.
- The onset of illness is often during late adolescence or early adult hood. It occurs in about 1% of the population and is a chronic and disabling disorder.
- Schizophrenia has a strong genetic component and probably reflects some fundamental biochemical abnormality, possibly a dysfunction of the mesolimbic or mesocortical dopaminergic neuronal pathways.

John Forbes Nash, Jr. (June 13, 1928 – May 23, 2015)
(Beautiful Mind)


Cortex
NAC
Striatum
Hypothalamus
SN
VTA
Pituitary
Mesocortical pathway
Mesolimbic pathway
Nigrostriatal pathway
Tuberoinfundibular pathway


Dopaminergic Pathways
Mesocortical
Prefrontal cortex
Mesolimbic
Nucleus accumbens
Nigrostriatal
Striatum
Behavior
(Negative Sx's)
Emotion
(Positive Sx's)
Movement
(Extrapyramidal SE via DA inhibition)
VTA
Tuberoinfundibular
Paraventricular n.
Infundibular (arcuate) n.
Median eminence
Dopamine inhibits prolactin release (Hyperprolactinemia via DA inhibition)
Dopamine Hypothesis Schizophrenia
Hypo-D1 activity in prefrontal cortex: Negative Sx's (eg, Apathy)
Hyper-D2 activity in limbic area: Positive Sx's (eg, Hallucinations)


Signs & Symptoms of Schizophrenia
Positive Symptoms
Negative Symptoms
Cognitive Symptoms
Hallucinations
Delusions
Disorganized speech and thoughts
Anhedonia
Avolition
Blunted affect
Memory issues
Inability to process social cues
Impaired sensory perception
verywell

The antipsychotic drugs

- The antipsychotic drugs are divided into first- (low and high potency) and second-generation agents (according to the specifies affinity for the dopamine D2 receptor, which, in turn, may influence the adverse effect profile of the drug.
- **A. First-generation antipsychotics (conventional, typical, or traditional antipsychotics):** Are competitive inhibitors at a variety of receptors, but their antipsychotic effects reflect competitive blocking of dopamine D2 receptors.

- First-generation antipsychotics are more likely to be associated with movement disorders known as extrapy ramidal symptoms (EPS), particularly drugs that bind tightly to dopaminergic neuroreceptors, such as haloperidol .
- Movement disorders are less likely with medications that bind weakly, such as chlorpromazine . No one drug is clinically more effective than another.

- **B. Second-generation antipsychotic drugs The second-generation antipsychotic drugs (also called "atypical" anti psychotics) :**
- **have a lower incidence of EPS than the first generation agents but are associated with a higher risk of metabolic side effects, such as diabetes, hypercholesterolemia, and weight gain.**
- **The second-generation drugs appear to owe their unique activity to blockade of both serotonin and dopamine and, perhaps, other receptors.**

- **The second-generation antipsychotics exhibit an efficacy that is equivalent to, and occasionally exceeds, that of the first-generation antipsychotic agents.**
- **However, consistent differences in therapeutic efficacy among the second-generation drugs have not been established, and individual patient response and comorbid conditions must often be used to guide drug selection.**

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. However, its clinical use is limited to refractory patients because of serious adverse effects.
- Clozapine can produce bone marrow suppression, seizures, and cardiovascular side effects, such as orthostasis. The risk of severe agranulocytosis necessitates frequent monitoring of white blood cell counts.

Mechanism of action

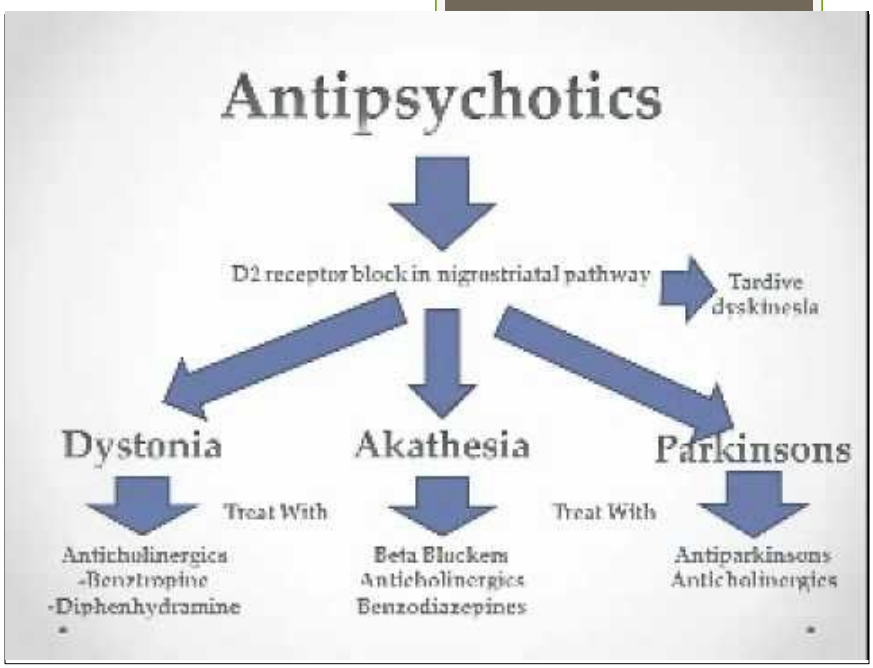
- 1. Dopamine antagonism: All of the first-generation and most of the second-generation antipsychotic drugs block D2 dopamine receptors in the brain and the periphery.
- 2. Serotonin receptor–blocking activity: Most of the second generation agents appear to exert part of their unique action through inhibition of serotonin receptors (5-HT), particularly 5-HT2A receptors.
- Clozapine has high affinity for D1 , D4 , 5-HT2 , muscarinic, and a-adrenergic receptors, but it is also a weak dopamine D2 receptor antagonist.
- The second-generation antipsychotic aripiprazole is a partial agonist at D2 and 5-HT1A receptors, as well as an antagonist of 5-HT2A receptors.
- Quetiapine blocks D2 receptors more potently than 5-HT2A receptors but is relatively weak at blocking either receptor. Its low risk for EPS may also be related to the relatively short period of time it binds to the D2 receptor.

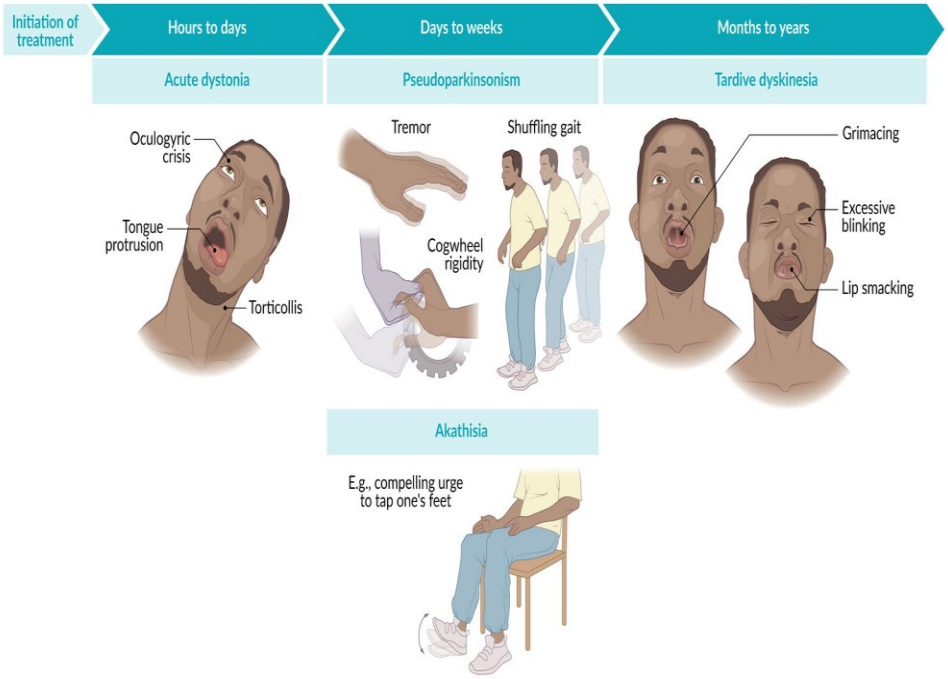
Antipsychotic effects of drugs

- 1st generation antipsychotic drugs can reduce hallu cinations and delusions associated with schizophrenia ("positive" symptoms) by blocking D2 receptors in the mesolimbic system of the brain.
- 2nd generation antipsychotics can reduce both positive and negative symptoms, and are more effective than 1st generation on negative symptoms such as blunted affect, apathy, and impaired attention, as well as cognitive impairment.
- Many second-generation agents, such as clozapine, can ameliorate the negative symptoms to some extent.

Extrapyramidal effects of drugs

- **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 second generation antipsychotics exhibit a lower incidence of EPS.





- It is better to monitor the patient closely to prevent the development of tardive dyskinesia that may be persistent.
- Treatment of tardive dyskinesia requires immediately withdraw the antipsychotic drug.
- Atypical antipsychotics such as olanzapine, risperidone or quetiapine are effective in tardive dyskinesia, and less likely to cause parkinsonism and restlessness.

Antiemetic effects of drugs: 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.

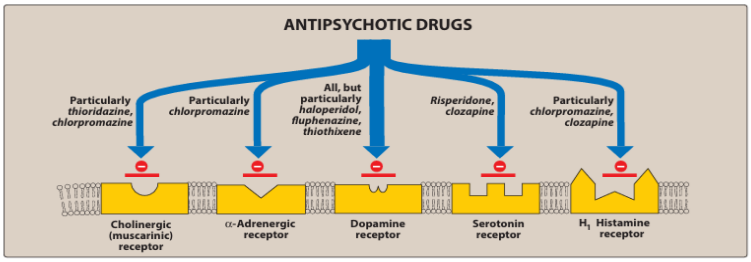


Figure 11.4
Antipsychotic drugs block at dopaminergic and serotonergic receptors as well as at adrenergic, cholinergic, and histamine-binding receptors.

- **Anticholinergic effects.**
- **Other effects:** Blockade of **a-adrenergic receptors** (orthostatic hypotension and light-headedness).
- 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 (increase prolactin release).
- **H1- blockade** (Sedation especially with chlorpromazine, olanzapine, quetiapine, and clozapine).
- ~~Sexual dysfunction (various receptor-binding).~~

Therapeutic uses

- 1. Treatment of schizophrenia:
- 2. Prevention of nausea and vomiting: The older antipsychotics (most commonly, prochlorperazine (Stemitel®) are useful in the treatment of drug-induced nausea).
- 3. Other uses: tranquilizers to manage agitated and disruptive behavior secondary to other disorders.
- Chlorpromazine is used to treat intractable hiccups.
- Pimozide, risperidone and haloperidol is primarily indicated for treatment of the motor and phonic tics of Tourette disorder.
- Also, risperidone and aripiprazole are approved for the management of disruptive behavior and irritability secondary to autism.
- Many anti psychotic agents are approved for the management of the manic and mixed symptoms associated with bipolar disorder.

Adverse effects

- Adverse effects of the antipsychotic drugs can occur in practically all patients and are significant in about 80%
- 1. Extrapyramidal effects: The appearance of the movement disorders is generally time and dose dependent, with dystonias occurring within a few hours to days of treatment, followed by akathisias occurring within days to weeks.
- Akathisia may respond better to β blockers (for example, propranolol) or benzodiazepines, rather than anticholinergic medications.
- Parkinson like symptoms of bradykinesia, rigidity, and tremor usually occur within weeks to months of initiating treatment. Finally, tardive dyskinesia.

- **2. Tardive dyskinesia (occures upon Long-term treatment):**
- **It can be irreversible, may occur after months or years of treatment.**
- **It is postulated to result from an increased number of dopamine receptors that are synthesized as a compensatory response to long-term dopamine receptor blockade. This makes the neuron supersensitive to the actions of dopamine, and it allows the dopaminergic input to this structure to overpower the cholinergic input, causing excess movement in the patient.**

- **If cholinergic activity is also blocked, a new, more nearly normal balance is restored, and extrapyramidal effects are minimized. This can be achieved by administration of an anticholinergic drug, such as benztropine.**
- **This effect is fewer with antipsychotics that exhibit strong anticholinergic activity, such as thioridazine). While Haloperidol and fluphenazin, have low anticholinergic activity and produce extrapyramidal effects more frequently because of the preferential blocking of dopaminergic transmission.**
- **Symptoms may be diminished within a few months by a prolonged holiday from antipsychotics. In many individuals, tardive dyskinesia is irreversible and persists after discontinuation of therapy.**

- **3. Neuroleptic malignant syndrome:** This potentially fatal reaction to antipsychotic drugs is characterized by muscle rigidity, fever, altered mental status and stupor, unstable blood pressure, and myoglobinemia. Treatment necessitates discontinuation of the antipsychotic agent and supportive therapy. Administration of dantrolene or bromocriptine may be helpful.
- **4. Cautions and contraindications:**
- lowerd the seizure threshold, increased risk for mortality when used in elderly patients with dementia-related behavioral disturbances and psychosis.
- Antipsychotics used in patients with mood disorders should also be monitored for worsening of mood and suicidal ideation or behaviors.

- **H. Maintenance treatment:**
- Patients who have had two or more psychotic episodes secondary to schizophrenia should receive maintenance therapy for at least 5 years, and some experts prefer indefinite therapy.
- Higher-dose maintenance therapy is required to prevent relapse.
- The rate of relapse may be lower with second-generation drugs.


THANK YOU.....