ANTIPSYCHOTIC DRUGS

The antipsychotic drugs (also called neuroleptics or major tranquilizers) are used primarily to treat schizophrenia, but they are also effective in other psychotic and manic states. The use of antipsychotic medications involves a difficult trade-off between the benefit of alleviating psychotic symptoms and the risk of a wide variety of troubling adverse effects. 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.

Psychosis (from the **Greek** , *psyche*, "mind ", and *-osis*, "abnormal condition or derangement") refers to an abnormal condition of the mind.

A syndrome of chronic disordered thinking and disturbed behavior (schizophrenia, mania, depression)

The most important types of psychosis are:

- Schizophrenia
- Affective disorders (e.g. depression, mania)
- Organic psychoses (mental disturbances caused by head injury, alcoholism, or other kinds of organic disease).

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.

Positive Symptoms of Schizophrenia

Hallucinations, delusions, paranoia, ideas of reference.

Negative Symptoms Schizophrenia

Apathy, social withdrawal, anhedonia, emotional blunting, Poor speech –Cognitive impairment, extreme inattentiveness or lack of motivation to interact with the environment.

Psychosis Producing Drugs:

1) *Levodopa*

2) *CNS stimulants*
    a) *Cocaine*
    b) *Amphetamines*
    c) *Khat, cathinone, methcathinone*
3) *Apomorphine*
4) *Phencyclidine*

Classification of antipsychotic drugs:

The antipsychotic drugs are divided into first- and second-generation agents. The first-generation drugs are further classified as “low potency” or “high potency.” This classification does not indicate clinical effectiveness of the drugs, but rather specifies affinity for the dopamine D2 receptor, which, in turn, may influence the adverse effect profile of the drug.

- **First generation ((Typical, traditional/older , classical , conventional)) Antipsychotics:**

1. Phenothiazines:

a. Aliphatic side chain: Chlorpromazine, Triflupromazine

b. Piperidine side chain: Thioridazine

c. Piperazine side chain: Trifluoperazine, perphenazine, Fluphenazine

2. Butyrophenones: Haloperidol, Trifluperidol, Penfluridol, droperidol, domperidone.

3. Thioxanthenes: Flupenthixo, thiothixene

4. Other heterocyclics: Pimozide, Loxapine, molindone, sulpiride, amisulpiride, Remoxipride.

- **Second generation ((Atypical/newer))antipsychotics: Clozapine, Risperidone, Olanzapine, Quetiapine, Aripiprazole, Ziprasidone, paloparidone.**

- **Note: typical antipsychotics with low potency include: Chlorpromazine, Thioridazine, prochlorperazine, promethazine.**
  While high potency antipsychotics include: Fluphenazine, Haloperidol, Pimozide

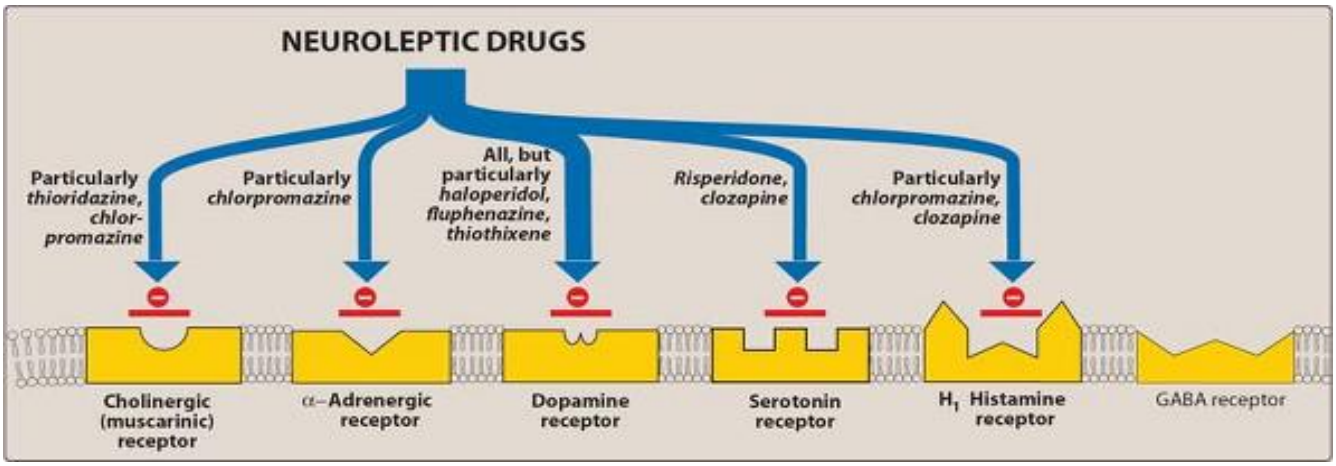
The first-generation antipsychotic drugs are competitive inhibitors at a variety of receptors, but their antipsychotic effects reflect competitive blocking of dopamine D2 receptors. First-generation antipsychotics are more likely to be associated with movement disorders known as extrapyramidal symptoms (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***.

While the second-generation antipsychotic drugs 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.

Second-generation agents are generally used as first-line therapy for schizophrenia to minimize the risk of debilitating EPS associated with the first-generation drugs that act primarily at the dopamine D2 receptor. The second-generation antipsychotics exhibit an efficacy that is equivalent to the first-generation antipsychotic drugs. 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. ((**Clozapine** has high affinity for D1, D4, 5-HT_2, muscarinic and **α**-adrenergic receptors, but it is also a weak dopamine D2 receptor antagonist)).

Mechanism of Action:

- All of the first-generation and most of the second-generation antipsychotic drugs block D2 receptors in the brain & periphery.
- Atypical antipsychotics exert part of their action through blocking of serotonin receptors ((5-HT_{2A})) receptors
- Additional mechanisms: antagonism on **α_1, M, H_1**



Pharmacokinetics:

After oral administration, the antipsychotics show variable absorption that is unaffected by food (except for ***ziprasidone*** and ***paliperidone***, the absorption of which is increased with food). Because they are lipid soluble, they readily enter the central nervous system (CNS) and most other body tissues. Many are bound extensively to plasma proteins. These drugs require metabolism by liver enzymes before elimination and have long plasma half-lives that permit once daily dosing. In some cases, other drugs that inhibit cytochrome P450 enzymes can prolong the half-lives of antipsychotic agents. Parenteral forms of many agents (e.g. **Fluphenazine decanoate**, **haloperidol decanoate**, **paliperidone palmitate** and **olanzapine pamoate**) are long-acting injectable (**LAI**) formulations of antipsychotics. These formulations have a therapeutic duration of action of up to 2 to 4 weeks and, therefore, are often used to treat out- patients and individuals who are non-adherent with oral medications). These drugs are available for both rapid initiation of therapy and depot treatment.

Therapeutic uses:

1. **Schizophrenia Rx (**The first-generation antipsychotics are most effective in treating positive symptoms of schizophrenia. The atypical antipsychotics may be effective in many patients who are resistant the traditional agents, especially in treating the negative symptoms of schizophrenia**).**
2. **Prevention of nausea and vomiting:** The older antipsychotics (most commonly, prochlorperazine) are useful in the treatment of drug-induced nausea.

3. **Mania (bipolar disorder): Initial Rx of Mania. Atypical antipsychotic drugs are often used with Lithium.**
4. **Treatment of chronic pain with severe anxiety in combination with opiates.**
5. **Hiccups: chlorpromazine**
6. **Antipruritus and sedation: promethazine**

Pharmacological actions:

Extrapyramidal effects: Dystonias (sustained contraction of muscles leading to twisting), 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.

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.

- Meclizine, Dimenhydrinate for tx. of nausea due to vertigo
- Scopolamine, promethazine for tx. Nausea due to motion sickness
- Haloperidol, metoclopramide, prochlorperazine for tx. of nausea due to cancer chemotherapy((drugs induced nausea))

Anticholinergic effects: Some of the antipsychotics, particularly *thioridazine*, *chlorpromazine*, *clozapine*, and *olanzapine*, produce anticholinergic effects. These effects include blurred vision, dry mouth (the exception is *clozapine*, which increases salivation), confusion, and inhibition of gastrointestinal and urinary tract smooth muscle, leading to constipation and urinary retention. The anticholinergic effects may actually assist in reducing the risk of EPS with these agents.

Other effects: Blockade of α-adrenergic receptors causes 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, 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*.

Adverse effects:

1. Reversible neurologic effects—Dose-dependent extrapyramidal effects include a Parkinson-like syndrome with bradykinesia, rigidity, and tremor. This toxicity may be reversed by a decrease in dose and may be antagonized by concomitant use of muscarinic blocking agents. Extrapyramidal toxicity occurs most frequently with haloperidol and the more potent piperazine side-chain phenothiazines (eg, fluphenazine, trifluoperazine). Parkinsonism occurs infrequently with clozapine and is much less common with the newer drugs. Other reversible neurologic dysfunctions that occur more frequently with older agents include akathisia and dystonias; these usually respond to treatment with diphenhydramine or muscarinic blocking agents.

2. Tardive dyskinesias—this important toxicity includes choreoathetoid movements of the muscles of the lips and buccal cavity and may be irreversible. Tardive dyskinesias tend to develop after several years of antipsychotic drug therapy but have appeared as early as 6 months. Antimuscarinic drugs that usually ameliorate other extrapyramidal effects generally *increase* the severity of tardive dyskinesia symptoms. There is no effective drug treatment for tardive dyskinesia. Switching to clozapine does not exacerbate the condition. Tardive dyskinesia may be attenuated *temporarily* by increasing neuroleptic dosage; this suggests that tardive dyskinesia may be caused by dopamine receptor sensitization.

3. Autonomic effects—Autonomic effects result from blockade of peripheral muscarinic receptors and α adrenoceptors and are more difficult to manage in elderly patients. Tolerance to some of the autonomic effects occurs with continued therapy. Of the older antipsychotic agents, thioridazine has the strongest autonomic effects and haloperidol the weakest. Clozapine and most of the atypical drugs have intermediate autonomic effects. Regarding muscarinic receptor blockade, atropine-like effects (dry mouth, constipation, urinary retention, and visual problems) are often pronounced with the use of thioridazine and phenothiazines with aliphatic side chains (eg, chlorpromazine). These effects also occur with clozapine and most of the atypical drugs but not with ziprasidone or aripiprazole. CNS effects from block of M receptors may include a toxic

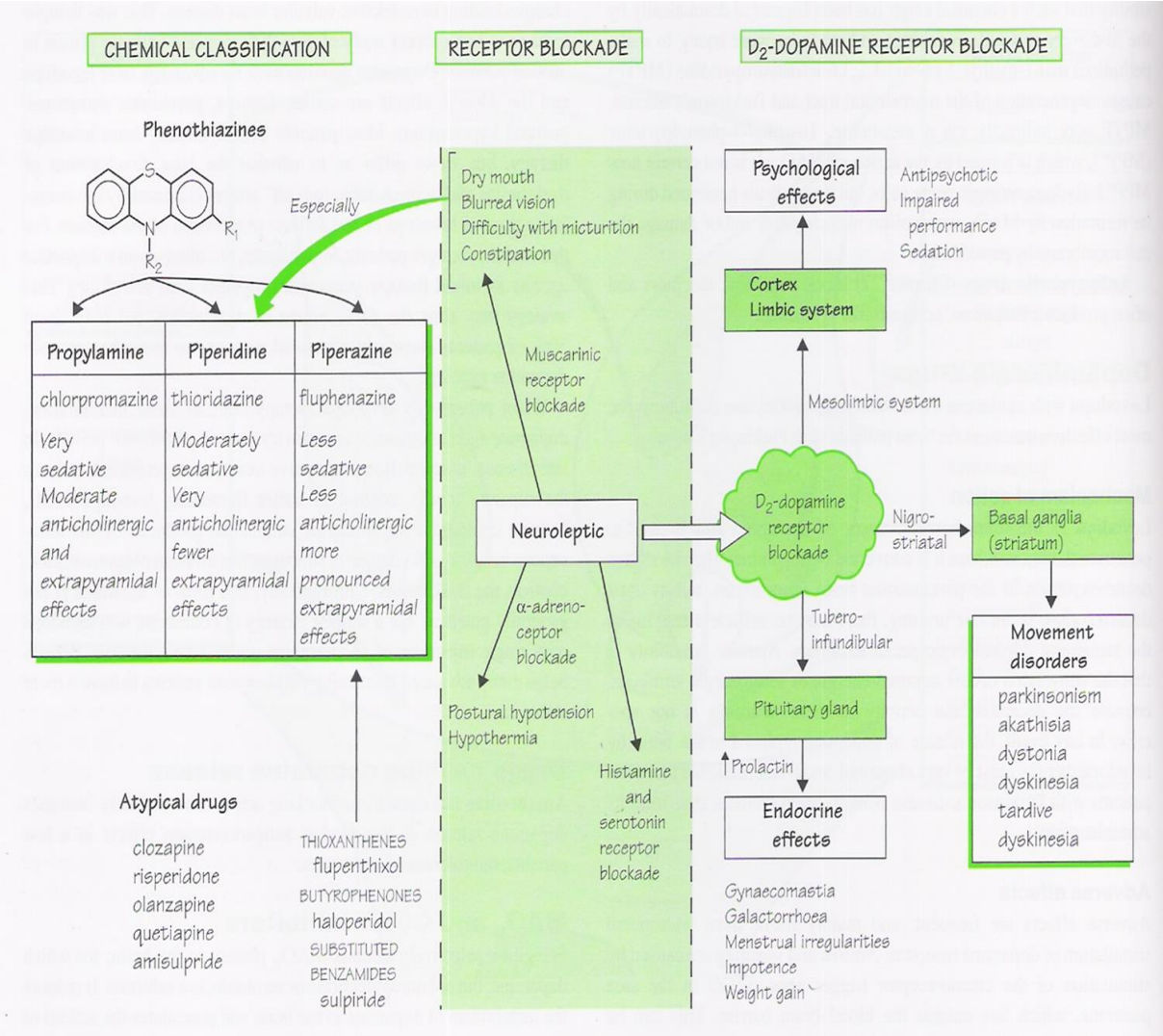
confusional state similar to that produced by atropine and the tricyclic antidepressants. Regarding α-receptor blockade, postural hypotension caused by α blockade is a common manifestation of many of the older drugs, especially phenothiazines.

4. Endocrine and metabolic effects—Endocrine and metabolic effects include hyperprolactinemia, gynecomastia, the amenorrhea-galactorrhea syndrome, and infertility. Most of these side effects are predictable manifestations of dopamine D2 receptor blockade in the pituitary; dopamine is the normal inhibitory regulator of prolactin secretion. 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. These effects may be especially problematic in pregnancy. Aripiprazole and ziprasidone have little or no tendency to cause hyperglycemia, hyperprolactinemia, or weight gain.

5. Neuroleptic malignant syndrome—Patients who are particularly sensitive to the extrapyramidal effects of antipsychotic drugs may develop a malignant hyperthermic syndrome. 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.

6. Sedation—This is more marked with phenothiazines (especially chlorpromazine) than with other antipsychotics; this effect is usually perceived as unpleasant by nonpsychotic persons. Fluphenazine and haloperidol are the least sedating of the older drugs; aripiprazole appears to be the least sedating of the newer agents.

- All antipsychotics may lower the seizure threshold and should be used cautiously in patients with seizure disorders or those with an increased risk for seizures, such as withdrawal from alcohol.
- Patients who have had two or more psychotic episodes secondary to schizophrenia should receive maintenance therapy for at least 5 years, Patients receiving the atypical antipsychotic risperidone show fewer relapses than those treated with haloperidol, a high- potency, typical antipsychotic.


CHEMICAL CLASSIFICATION
RECEPTOR BLOCKADE
D2-DOPAMINE RECEPTOR BLOCKADE
Phenothiazines
Especially
Propylamine
Piperidine
Piperazine
chlorpromazine
thioridazine
fluphenazine
Very sedative Moderate anticholinergic and extrapyramidal effects
Moderately sedative Very anticholinergic fewer extrapyramidal effects
Less sedative Less anticholinergic more pronounced extrapyramidal effects
Atypical drugs
clozapine
risperidone
olanzapine
quetiapine
amisulpride
THIOXANTHENES
flupenthixol
BUTYROPHENONES
haloperidol
SUBSTITUTED BENZAMIDES
sulpiride
Dry mouth
Blurred vision
Difficulty with micturition
Constipation
Muscarinic receptor blockade
Neuroleptic
α-adreno-ceptor blockade
Postural hypotension
Hypothermia
Histamine and serotonin receptor blockade
Psychological effects
Antipsychotic
Impaired performance
Sedation
Cortex
Limbic system
Mesolimbic system
D2-dopamine receptor blockade
Nigro-striatal
Basal ganglia (striatum)
Movement disorders
parkinsonism
akathisia
dystonia
dyskinesia
tardive dyskinesia
Tubero-infundibular
Pituitary gland
Prolactin
Endocrine effects
Gynaecomastia
Galactorrhoea
Menstrual irregularities
Impotence
Weight gain

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