ANTI PSYCHOTIC DRUGS

From Lippincott

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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.

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 adulthood. It occurs in about 1% of the population and is a chronic and disabling disorder

	FIRST GENERATION (Typical, Conventional)		**SECOND GENERATION (Atypical)**
DRUG NAMES	**LOW POTENCY** Chlorpromazine Thioridazine	**HIGH POTENCY** Fluphenazine Haloperidol Loxapine Molindone Perphenazine Pimozide Prochlorperazine Thiothixene Trifluoperazine	Ariprazole Asenapine Brexpiprazole Cariprazine Clozapine Iloperidone Lurasidone Olanzapine Paliperidone Pimavenserin Quetiapine Risperidone Ziprasidone
MOA	competitive blocking of dopamine D2 receptors.		blockade of both serotonin and dopamine receptors.

ADVERSE EFFECTS	- movement disorders known as extrapyramidal symptoms (EPS), particularly with drugs that bind tightly to dopaminergic neuroreceptors, such as haloperidol	- 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.
THERAPEUTIC USES	-Tx of schizophrenia -The older antipsychotics (most commonly, prochlorperazine) are useful in the treatment of drug-induced nausea - Chlorpromazine is used to treat intractable hiccups. - Pimozide is primarily indicated for treatment of the motor and phonic tics of Tourette disorder. However, risperidone and haloperidol are also commonly prescribed for this tic disorder.	- first-line therapy for schizophrenia to minimize the risk of debilitating EPS associated with the first-generation drugs - Risperidone and aripiprazole are approved for the management of disruptive behavior and irritability secondary to autism. - Lurasidone and quetiapine are indicated for the treatment of bipolar depression. - Paliperidone is approved for the treatment of schizoaffective disorder. - Aripiprazole and quetiapine are used as adjunctive agents with antidepressants for treatment of refractory depression
OTHER POINTS		-Approximately 10% to 20% of patients with schizophrenia have an insufficient response to all first- and secondgeneration 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.

ADVERSE EFFECTS OF ANTI PSYCHOTIC DRUGS:

Adverse effects of the antipsychotic drugs can occur in practically all patients and are significant in about 80%

- 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.
- The “negative” symptoms, such as blunted affect, apathy, and impaired attention, as well as cognitive impairment, are not as responsive to therapy, particularly with the first-generation antipsychotics. Many second-generation agents, such as clozapine, can ameliorate the negative symptoms to some extent.
- 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
- 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.
- Sexual dysfunction may also occur with the antipsychotics due to various receptor-binding characteristics.
- Drowsiness occurs due to CNS depression and antihistaminic effects, usually during the first few weeks of treatment.
- The antipsychotics depress the hypothalamus, affecting thermoregulation and causing amenorrhea, galactorrhea, gynecomastia, infertility, and erectile dysfunction. Significant weight gain is often a reason for nonadherence.
- 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.
- These agents also carry the warning of 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.

Extrapyramidal effects: The inhibitory effects of dopaminergic neurons are normally balanced by the excitatory actions of cholinergic neurons in the striatum. Blocking dopamine receptors alters this balance, causing a relative excess of cholinergic influence, which results in extrapyramidal motor 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.

Parkinson like symptoms of bradykinesia, rigidity, and tremor usually occur within weeks to months of initiating treatment. Tardive dyskinesia, which can be irreversible, may occur after months or years of treatment.
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. The therapeutic trade-off is a lower incidence of EPS in exchange for the side effect of muscarinic receptor blockade. Those antipsychotic drugs that exhibit strong anticholinergic activity, such as thioridazine, show fewer extrapyramidal disturbances, because the cholinergic activity is already strongly dampened. This contrasts with haloperidol and fluphenazine, which have low anticholinergic activity and produce extrapyramidal effects more frequently because of the preferential blocking of dopaminergic transmission. Akathisia may respond better to β blockers (for example, propranolol) or benzodiazepines, rather than anticholinergic medications

Tardive dyskinesia: Long-term treatment with antipsychotics can cause this motor disorder. Patients display involuntary movements, including bilateral and facial jaw movements and “fly-catching” motions of the tongue. A prolonged holiday from antipsychotics may cause the symptoms to diminish or disappear within a few months. However, in many individuals, tardive dyskinesia is irreversible and persists after discontinuation of therapy. Tardive dyskinesia 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. Traditional anti-EPS medications may actually worsen this condition.

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

THERAPEUTIC USES OF ANTI PSYCHOTIC DRUGS:

- Treatment of schizophrenia
- All antipsychotic drugs can reduce hallucinations and delusions associated with schizophrenia (known as “positive” symptoms) by blocking D2 receptors in the mesolimbic system of the brain.
- 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
- The antipsychotic drugs can be used as tranquilizers to manage agitated and disruptive behavior secondary to other disorders.

- Many antipsychotic agents are approved for the management of the manic and mixed symptoms associated with bipolar disorder.