Antipsychotic Agents

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Antipsychotic Agents

Nature of Psychosis & Schizophrenia:

- **The term "psychosis" denotes a variety of mental disorders characterized by the inability to distinguish between what is real and what is not: the presence of delusions (false beliefs); various types of hallucinations (auditory, visual, tactile or olfactory); and grossly disorganized thinking in a clear sensorium. (Marked thinking and perceptual disturbance)**

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A. The Serotonin Hypothesis of Schizophrenia:

- **Hallucinogens such as LSD and mescaline are serotonin agonists, at 5-HT_{2A}- and possibly 5-HT_{2C} receptors.**
- **5-HT_{2A}-receptor blockade is the main mechanism of action of the second-generation antipsychotic drugs (clozapine and others).**

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- **5-HT_{2A} receptors modulate the release of dopamine, norepinephrine, glutamate, GABA, and acetylcholine, and other neurotransmitters in the cortex, limbic system, and striatum.**
- **Stimulation of 5-HT_{2C} receptors leads to inhibition of cortical and limbic dopamine release.**

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B. The Dopamine Hypothesis for Schizophrenia:

- **It is no longer considered adequate to explain all aspects of schizophrenia.**
- **Nevertheless, it is still highly relevant to understanding hallucinations, delusions, emotional blunting, social withdrawal, lack of motivation, cognitive impairment & possibly depression, and understanding the mechanisms of action of most antipsychotic drugs.**

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- **Evidence suggesting that excessive limbic dopaminergic activity plays a role in psychosis:**

1. **Many antipsychotic drugs strongly block postsynaptic D_2 receptors in the central nervous system, especially in the mesolimbic and striatal-frontal system.**

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2. Drugs that increase dopaminergic activity, such as levodopa, amphetamines, bromocriptine and apomorphine, either aggravate schizophrenia psychosis or produce psychosis in some patients.
3. Dopamine-receptor density has been found postmortem to be increased in the brains of schizophrenics who have not been treated with antipsychotic drugs. Increased dopamine levels and D_2 -receptor density in the nucleus accumbens, caudate, and putamen.

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Evidence against:

A. **Several of the atypical antipsychotic drugs have much less effect on D_2 receptors and yet are effective in schizophrenia.**

B. **The atypical antipsychotic drugs share the property of weak D_2-receptor antagonism and more potent $5\text{-}HT_{2A}$-receptor blockade.**

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C. The Glutamate Hypothesis of Schizophrenia:

- **Antagonists of NMDA receptor such as phencyclidine and ketamine (non-competative) exacerbate both cognitive impairment and psychosis in patients with schizophrenia.**

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Classification:

A. Firs-Generation Antipsychotic Drugs:

1. **Phenothiazine derivatives:**
   Chloropromazine, thioridazine, and perphenazine.
2. **Thioxanthine derivatives: Thiothixene.**
3. **Butyrophenone derivatives: Haloperidol.**
3. **Miscellaneous Agents: Pimozide**

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B. Second-Generation Antipsychotic Drugs:

- **Clozapine, olanzapine, quetiapine, risperidone, cariprazine, aripiprazole, and sulpride …..**

C. Glutamatergic Antipsychotics: investigational.

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Pharmacokinetics:

- Most antipsychotics are readily but incompletely absorbed.
- Many undergo significant first-pass metabolism.
- Most are highly lipid soluble, and highly protein-bound (92-99%).
- They tend to have large volumes of distribution (> 7L/Kg).

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- **They have a much longer duration of action than that anticipated from their half-lives (sequestered in body fat, and prolonged occupancy of D_2 dopamine receptors in the brain of typical antipsychotic drugs).**

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- **Full relapse may not occur until 6 weeks or more after discontinuation of many antipsychotics.**
- **Clozapine is an exception, relapse after discontinuation is usually rapid and severe.**
- **Thus, clozapine should never be discontinued abruptly unless clinically needed because of adverse effects such as myocarditis or agranulocytosis.**

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- **Most antipsychotics are almost completely metabolized.**
- **Cytochrome P450 enzymes (CYP2D6, CYP1A2, and CYP3A4) are the major isoforms involved.**
- **Mesoridazine, the major metabolite of thioridazine, is more potent than the parent compound and accounts for most of the effect.**

TABLE 29–1 Antipsychotic drugs: Relation of chemical structure to potency and toxicities.

Chemical Class	Drug	D_2/5-HT_{2A} Ratio[1]	Clinical Potency	Extrapyramidal Toxicity	Sedative Action	Hypotensive Actions
Phenothiazines						
Aliphatic	Chlorpromazine	High	Low	Medium	High	High
Piperazine	Fluphenazine	High	High	High	Low	Very low
Thioxanthene	Thiothixene	Very high	High	Medium	Medium	Medium
Butyrophenone	Haloperidol	Medium	High	Very high	Low	Very low
Dibenzodiazepine	Clozapine	Very low	Medium	Very low	Low	Medium
Benzisoxazole	Risperidone	Very low	High	Low[2]	Low	Low
Thienobenzodiazepine	Olanzapine	Low	High	Very low	Medium	Low
Dibenzothiazepine	Quetiapine	Low	Low	Very low	Medium	Low to medium
Dihydroindolone	Ziprasidone	Low	Medium	Very low	Low	Very low
Dihydrocarbostyril	Aripiprazole	Medium	High	Very low	Very low	Low

[1] Ratio of affinity for D_2 receptors to affinity for 5-HT_{2A} receptors.

[2] At dosages below 8 mg/d.

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Pharmacodynamics:

Dopaminergic systems:

5 pathways are found in the brain:

1. **Mesolimbic-mesocortical pathway which is closely related to behavior and psychosis.**
2. **Nigrostriatal pathway which is involved in the coordination of voluntary movement.**

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3. Tuberoinfundibular system. Dopamine released by these neurons inhibits prolactin secretion from the anterior pituitary.
4. The medullary-periventricular pathway which may be involved in eating behavior.
5. The incertohypothalamic pathway. (Function ??). It may regulate the anticipatory motivational phase of copulatory behavior (??).

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- **The antipsychotic action is thought to be produced, at least in part, by their ability to block dopamine in the mesolimbic and mesocortical systems.**
- **The antagonism of dopamine in the nigrostriatal system explains parkinsonism produced by these drugs as an adverse effect.**

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- **The hyperprolactinemia produced by antipsychotics during treatment is caused by blockade of the inhibitory effect of dopamine on prolactin.**

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Differences among Antipsychotic Drugs:

Chlorpromazine: $\alpha_1 = 5\text{-}HT_{2A} > D_2 > D_1$

Haloperidol: $D_2 > \alpha_1 > D_4 > 5\text{-}HT_{2A} > D_1 > H_1$

Clozapine: $D_4 = \alpha_1 > 5\text{-}HT_{2A} > D_2 = D_1$

Olanzapine: $5\text{-}HT_{2A} > H_1 > D_4 > D_2 > \alpha_1 > D_1$

Aripiprazole: $D_2 = 5\text{-}HT_{2A} > D_4 > \alpha_1 = H_1 >> D_1$

Quetiapine: $H_1 > \alpha_1 > M_{1,3} > D_2 > 5\text{-}HT_{2A}$

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Pharmacological effects:

1. **Psychological effects:**

- **Most antipsychotics cause unpleasant subjective effects in nonpsychotic individuals: sleepiness, restlessness, autonomic effects, and impaired performance.**
- **Psychotic individuals show improvement in performance as their psychosis is alleviated.**

2. **Some antipsychotics lower seizure threshold.**

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3. Endocrine effects:

- **Older typical antipsychotic drugs, as well as risperidone and paliperidone, produce elevations of prolactin.**
- **Amenorrhea-galactorrhea, false-positive pregnancy tests, and increased libido have been reported in women.**
- **Men have experienced decreased libido and gynecomastia.**

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- **Newer antipsychotics such as olanzapine, quetiapine, and aripiprazole cause no or minimal increases of prolactin.**

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4. Cardiovascular effects:

- **Phenothiazines frequently cause orthostatic hypotension and tachycardia. Mean arterial pressure, peripheral resistance, and stroke volume are decreased.**
- **Thioridazine prolongs QT intervals with increased risk of dangerous arrhythmias. It is associated with torsades de pointes and an increased risk of sudden death (2nd line drug).**

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- **The atypical antipsychotics are also associated with a metabolic syndrome that may increase the risk of coronary artery disease, stroke, and hypertension.**

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Therapeutic uses:

A. Psychiatric indications:

1. **Schizophrenia.**
2. **Bipolar affective disorder (manic phase with lithium, or valproic acid + lorazepam), or monotherapy with a second generation antipsychotic.**

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B. Nonpsychiatric indications:

1. Antiemetics – prochlorperazine and benzquinamide

2. Relief of pruritus (H_1-blockers – promethazine).

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Adverse Reactions:

- **Most are extension of their pharmacologic actions, and few are idiosyncratic.**

A. Behavioral effects:

1. The older agents are unpleasant to take. It is preferred to give small portion of the dose during the day, and the major portion at bedtime.

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2. “Pseudodepression” that might be due to drug-induced akinesia. It responds to dose reduction or antiparkinsonism drugs.

3. Toxic confusional state may occur with very high doses of drugs with antimuscarinic actions.

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B. Neurologic effects:

1. Extrapyramidal reactions occur early during treatment with older agents, and include:

a. Parkinson's syndrome (may be self-limiting), can be treated with antimuscarinic drugs or with amantadine. Levodopa should never be used in these patients.

b. Akathisia (uncontrollable restlessness, unable to sit).

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c. Acute dystonic reactions (spastic torticolis, a condition in which the head is tilted toward one side, and the chin is elevated and turned toward the opposite side).

- Akathisia and dystonic reactions may be treated by antimuscarinic drugs or with amantadine, but it is preferable to use a sedative antihistamine with anticholinergic action (diphenhydramine).

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2. Tardive dyskinesia (repetitive, involuntary, purposeless movements). Features of the disorder may include grimacing, tongue protrusion, lip smacking, puckering and pursing of the lips, and rapid eye blinking. Rapid movements of the arms, legs, and trunk may also occur.

- **It is the most important adverse effect of antipsychotics.**

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- **Proposed to be caused by a relative cholinergic deficiency secondary to supersensitivity of dopamine receptors in the caudate-putamen.**
- **It has occurred in 20-40% of chronically treated patients with the older antipsychotics.**

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- **The first step of treatment of tardive dyskinesia is to stop the drug or reduce the dose.**
- **The second step is to eliminate all drugs with central anticholinergic actions (antiparkinsonism drugs and tricyclic antidepressants).**
- **Patients treated with old antipsychotics should be switched to quetiapine or clozapine.**
- **If these steps fail, add diazepam.**

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3. **Seizures: rare, but may occur in 2-5% of patients treated with clozapine.**

C. **Autonomic nervous system effects:**

   1. Antimuscarinic actions (?).

   2. Orthostatic hypotension.

   3. Impaired ejaculation (adrenoceptor blockers).

   4. Urine retention.

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D. Metabolic and endocrine effects:

1. **Weight gain is common with clozapine and olanzapine.**
2. **Hyperglycemia.**
3. **Hyperlipidemia**
4. **Hyperprolactinemia → amenorrhea-galactorrhea and infertility in women, and loss of libido, impotence and infertility in men. Switch to agents that do not increase prolactin (aripiprazole).**

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E. Toxic and allergic reactions:

Agranulocytosis, cholestatic jaundice, and skin eruption.

Patients receiving clozapine must have weekly blood counts for the first 6 months of therapy, and every 3 weeks thereafter.

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F. Ocular complications:

- **Deposits in the cornea and lens are common with chloropromazine therapy.**
- **Thioridazine is the only antipsychotic that has caused retinal deposits → browning of vision. The maximum daily dose of this drug has been limited to 800 mg to reduce this complication.**

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G. Cardiac toxicity:

- **Minor abnormalities of T wave (thioridazine).**
- **Overdoses (thioridazine) → major ventricular arrhythmias, cardiac conduction block, and sudden death.**
- **Ziprasidone has the greater risk of QT prolongation. It should not be combined with other drugs that prolong the QT interval (thioridazine, pimozide).**

- **Clozapine may cause myocarditis.**

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H. Use in Pregnancy:

- May increase teratogenic risk.

I. Neuroleptic malignant syndrome:

- Occur with antipsychotics having extrapyramidal adverse effects.
- Marked muscle rigidity, fever, stress leukocytosis (confused with meningitis).
- Autonomic instability with altered blood pressure and heart rate.

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- **Elevation of creatine kinase isoenzymes.**
- **The syndrome is thought to be caused by excessively rapid blockade of postsynaptic dopamine receptors.**

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- **Treatment: muscle relaxants (diazepam, dantrolene), dopamine agonists (bromocriptine) and reduce fever.**
- **Switching to an atypical drug after recovery is indicated.**

Drug Interactions:

- **With sedatives, anticholinergic drugs and α-adrenoceptor blockers, ..**