Antipsychotics

- Antipsychotic drugs = Neuroleptics= Major tranquilizers

Drugs that are primarily used to treat schizophrenia

- They can also be used for other psychotic states including manic states with psychotic symptoms such as grandiosity, paranoia and hallucinations

- Use of antipsychotics involves benefits of alleviating psychotic symptoms and the risk of troubling adverse effects
- Antipsychotic drugs are not curative and do not eliminate the chronic thought disorder
- These drugs decrease the intensity of hallucinations and delusions and permit the person with schizophrenia to function in a supportive environment

- Psychosis: a mental disorder caused by brain dysfunction
- Schizophrenia
  - Type of psychosis characterized by:
    - Delusions
    - Hallucinations (often in the form of voices)
    - Thinking or speech disturbances
  - Schizophrenia is a chronic and disabling disorder
  - Occurs in 1% of population
  - It has a genetic component
  - Biochemical abnormalities include dysfunction of dopaminergic pathways
  - Associated with D_2 type of dopamine receptor

Diagnostic Criteria for Schizophrenia

- At least two of the characteristic symptoms:
  - Delusions
  - Hallucinations
  - Disorganized thoughts and speech
  - Grossly disorganized behavior
  - Negative symptoms (blunted affect, anhedonia, apathy, social isolation, poor hygiene, poor memory, impaired attention and poor cognition)
- Deterioration in function
- Duration at least 6 months

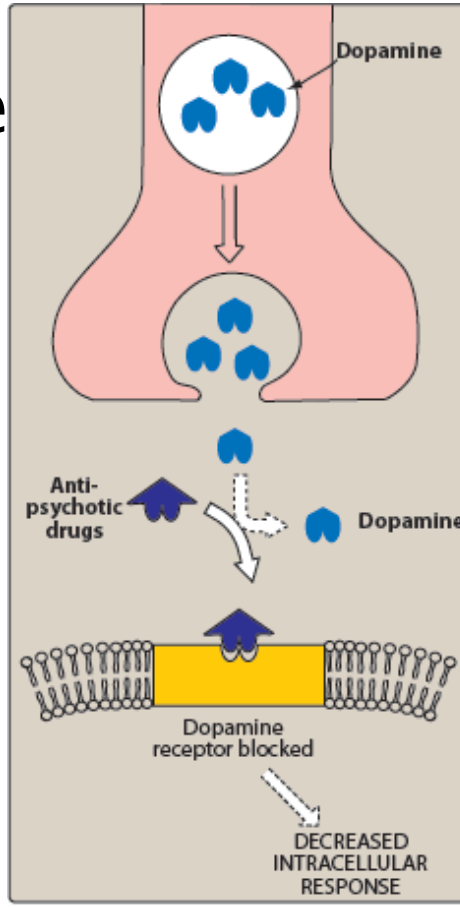
Antipsychotic drugs

- Affect dopamine by blocking dopamine receptors

- First generation antipsychotics
  - low potency
  - high potency

Based on their affinity for D2 receptors which influences side effects

- Second generation antipsychotics



First-generation antipsychotics

- Low potency
  - Chlorpromazine
  - Thioridazine
- High potency
  - Haloperidol
  - Fluphenazine
  - Pimozide
  - Prochlorperazine
  - Thiothixene
  - Trifulperazine

First generation antipsychotics

- Also called conventional, typical or traditional antipsychotics
- Competitive blockers of D_2 receptors
- Associated with movement disorders, especially the ones with stronger binding to dopamine receptors
- No drug is clinically more effective than the other

Second-generation antipsychotics

- Aripiprazole
- Brexpiprazole
- Lurasidone
- Paliperidone
- Risperidone
- Ziprasidone
- Asenapine
- Cariprazine
- Olanzapine
- Quetiapine
- Clozapine

Second generation antipsychotics

- Preferred to minimize the risk of debilitating movement disorders associated with first generation
- Efficacy is equivalent to and occasionally exceeds, that of the first-generation
- No differences in therapeutic efficacy among second-generation drugs
- Individual patient response and comorbid conditions must often be considered in drug selection
- Second-generation antipsychotics are not interchangeable because patients may respond differently to each drug

Second generation antipsychotics

- 20% of patients with schizophrenia will have an insufficient response to all first- and second generation antipsychotics and clozapine has shown to be effective for these patients
- Clozapine use is limited to refractory patients because of serious side effects:
  - Bone marrow suppression

  (frequent monitoring of white blood cell counts is required due to risk of severe agranulocytosis)
  - Seizures
  - Cardiovascular side effects

Second generation antipsychotics

- Also referred to as atypical antipsychotics
- Have fewer EPS than first generation drugs
- Associated with a higher risk of metabolic side effects like diabetes, hypercholesterolemia and weight gain
- Block both dopamine and serotonin receptors

Antipsychotics

Actions

- The antipsychotic actions are due to blockade at dopamine and/or serotonin receptors
- Many of these agents also block cholinergic, adrenergic, and histaminergic receptors causing adverse effects

1. Antipsychotic actions
2. Extrapyramidal effects
3. Antiemetic effects
4. Anticholinergic effects
5. Other effects

Antipsychotics

Antipsychotic actions:

- All antipsychotics can reduce the hallucinations and delusions associated with schizophrenia ("positive" symptoms) by blocking dopamine receptors in the mesolimbic system of the brain
- The "negative" symptoms, such as blunted affect, anhedonia, apathy, impaired attention, and cognitive impairment are not as responsive to therapy, particularly with the first-generation
- Many second-generation agents, such as clozapine, ameliorate the negative symptoms
- All of the drugs also have a calming effect and reduce spontaneous physical movement without depressing the intellectual functioning of the patient
- The antipsychotic effects take several days to weeks

Antipsychotics

2. Extrapyramidal effects:

- Dystonias (sustained contraction of muscles leading to twisting, distorted postures)
- Parkinson-like symptoms
  - Akathisia (motor restlessness)
  - Tardive dyskinesia (involuntary movements of the tongue, lips, neck, trunk, and limbs)
  - Occur with chronic treatment due to blocking of dopamine receptors in the nigrostriatal pathway
- The second-generation antipsychotics exhibit a lower incidence of these symptoms

Antipsychotics

3. Antiemetic effects:

- Most antipsychotic drugs have antiemetic effects that are mediated by blocking D_2-dopaminergic receptors of the chemoreceptor trigger zone of the medulla
- Domperidone, haloperidol, prochlorperazine are used for nausea due to chemotherapy
- Thiethylperazine and domeperidone are used for nausea due to radiation therapy
- Second-generation antipsychotic drugs are not used as antiemetics

Antipsychotics

4. Anticholinergic effects:

- Some antipsychotics particularly thioridazine, chlorpromazine, clozapine, and olanzapine produce anticholinergic effects, including blurred vision; dry mouth
- This anticholinergic property may actually assist in reducing the risk of EPS with these agents
- Clozapine is an exception, it increases salivation; confusion; and inhibits gastrointestinal and urinary tract smooth muscle, leading to constipation and urinary retention

Antipsychotics

5. Other effects

- Blockade of α-adrenergic receptors causing orthostatic hypotension
- In the pituitary, antipsychotics block D_2 receptors, leading to an increase in prolactin release
- Second-generation antipsychotics are less likely to produce prolactin elevations
- Sedation occurs with drugs that are potent antagonists of the H1-histamine receptor, including chlorpromazine, olanzapine, quetiapine, and clozapine
- Sexual dysfunction may also occur

Antipsychotic drugs

Therapeutic uses

1. Treatment of schizophrenia
2. Prevention of severe nausea and vomiting:
   - Antipsychotics like prochlorperazine are useful in the treatment of drug-induced emesis (e.g. chemotherapy)
3. Used as tranquilizers to manage agitated and disruptive behavior secondary to other disorders
4. Used in combination with narcotic analgesics for treatment of chronic pain with severe anxiety
5. Chlorpromazine is used to treat intractable hiccups
6. Risperidone and aripiprazole are now approved for management of the disruptive behavior and irritability secondary to autism

Antipsychotics

- Metabolized by the cytochrome P450 system in the liver: CYP2D6, CYP1A2, and CYP3A4
- Some metabolites are active

Antipsychotics

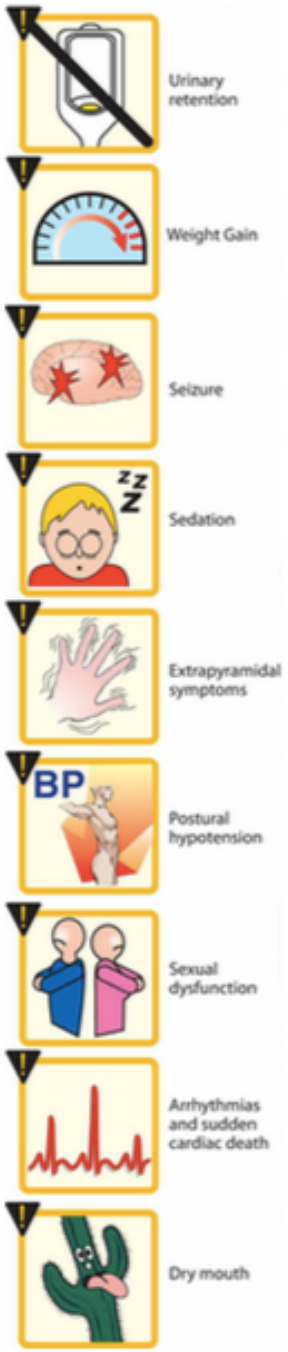
Adverse effects

1. Extrapyramidal side effects: due to blockade of dopamine receptors
   - The maximal risk of movement disorders is time and dose dependent
   - Administration of an anticholinergic drug, such as benztropine minimizes EPS
2. Tardive dyskinesia:
   - Due to long-term treatment with antipsychotics
   - Involuntary movements
   - A prolonged holiday from antipsychotics may cause the symptoms to diminish or disappear
   - Can be irreversible
   - Caused by an increased number of dopamine receptors that are synthesized as a compensatory response to long-term dopamine-receptor blockade causing excess movement in the patient
3. Antipsychotic malignant syndrome: (Potentially fatal)
   - Muscle rigidity, fever, altered mental status , unstable blood pressure
   - Treatment necessitates discontinuation of the antipsychotic agent and supportive therapy, administration of dantrolene or bromocriptine may be helpful

Antipsychotics

Adverse effects

4. Drowsiness occurs due to CNS depression and antihistaminic effects
5. Antimuscarinic activity produces dry mouth, urinary retention, constipation
6. Blocking α-adrenergic receptors results in orthostatic hypotension
7. The antipsychotics depress the hypothalamus, affecting thermoregulation and causing amenorrhea, galactorrhea, gynecomastia, infertility, and impotence
8. Weight gain
9. Hyperglycemia and hypercholesterolemia (second-generation atipsychotics); Glucose and lipid profiles should be monitored
10. Clozapine causes agranulocytosis



Antipsychotics

- 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
- Low doses of antipsychotic drugs are not as effective as higher-dose maintenance therapy in preventing relapse
- The rate of relapse may be lower with second generation drugs

DRUG	THERAPEUTIC NOTES
First generation	
Chlorpromazine	Moderate to high potential for EPS; moderate to high potential for weight gain, orthostasis, sedation, anti-muscarinic effects.
Fluphenazine	Oral formulation has a high potential for EPS; low potential for weight gain, sedation, and orthostasis; low to moderate potential for antimuscarinic effects; common use is in the LAI formulation administered every 2–3 weeks in patients with schizophrenia and a history of noncompliance with oral antipsychotic regimens.
Haloperidol	High potential for EPS; low potential for anti-adrenergic (orthostasis) or antimuscarinic adverse events; low potential for weight gain or sedation; available in a LAI formulation administered every 4 weeks.
Second generation	
Aripiprazole	Low potential for EPS; low potential for weight gain; low potential for sedation and antimuscarinic effects; also approved for the treatment of bipolar disorder; also approved for autistic disorder in children, and as an adjunctive treatment for major depression; two LAI formulations are available.
Asenapine	Low potential for EPS; low potential for weight gain; low to moderate potential for sedation; low potential for orthostasis; also approved for the treatment of bipolar disorder; available as a sublingual formulation.
Brexpiprazole	Low potential for EPS; low potential for weight gain; low potential for sedation; also approved as an adjunctive treatment for partial response or refractory major depression with an antidepressant.
Cariprazine	Low potential for EPS; low potential for weight gain; possible nausea and gastrointestinal distress; also approved for manic/mixed episodes associated with bipolar disorder.
Clozapine	Very low potential for EPS; risk for blood dyscrasias (for example, agranulocytosis = ~1%); risk for seizures; risk for myo-carditis; high potential for the following: sialorrhea, weight gain, antimuscarinic effects, orthostasis, and sedation.
Lurasidone	Low potential for EPS; minimal weight gain; also approved for use in treating depression associated with bipolar disorder; food increases absorption.
Olanzapine	Low potential for EPS; moderate to high potential for weight gain and sedation; low potential for orthostasis; also approved for the treatment of bipolar disorder; available as a LAI formulation administered every 2–4 weeks.
Paliperidone	Low to moderate potential for EPS; low potential for weight gain; low potential for sedation; available as a LAI formulation administered every 4 weeks and as an alternate LAI formulation administered every 12 weeks; also approved for use in schizoaffective disorder.
Quetiapine	Low potential for EPS; moderate potential for weight gain; moderate potential for orthostasis; moderate to high potential for sedation; also approved for the treatment of bipolar disorder and as an adjunctive treatment for major depression.
Risperidone	Low to moderate potential for EPS; low to moderate potential for weight gain; low to moderate potential for orthostasis; low to moderate potential for sedation; also approved for the treatment of bipolar disorder; also approved for autistic disorder in children; available as a LAI formulation administered every 2 weeks.
Ziprasidone	Low potential for extrapyramidal effects; contraindicated in patients with history of cardiac arrhythmias; minimal weight gain. Used in treatment of bipolar depression.

Figure 11.8 Summary of antipsychotic agents commonly used to treat schizophrenia. EPS = extrapyramidal effects; LAI = long-acting injectable.