Antipsychotic Drugs

Used for tx of SZ and for the tx of psychotic sx in manic states, major depression, dementia, delirium, and drug-induced psychoses

Antipsychotic Drug Groups:

➤ 1st generation antipsychotic agents (Typical)

➤ 2nd generation (Atypical)

Can treat both organic and drug-induced

Prototypical 1st Generation (Typical)

Low Potency	**Chlorpromazine** (1st antipsychotic discovered)
	Thioridazine
Medium Potency	Loxapine
	Perphenazine
High Potency	**Haloperidol**
	Droperidol
	Fluphenazine
	Pimozide

Chlorpromazine

Very 1st antipsychotic drug discovered

Prototypic, low-potency drug (*now, rarely used as an antipsychotic agent*)

Has **Low** affinity for D2 receptors

Main Side Effects: orthostatic hypotension (alpha 1 receptor blockade), sedation (H1), and weight gain (H1 and 5-HT-2A)

LOW incidence of EPS (*low affinity for D2*)

Dermatological reactions (urticaria and photosensitivity resembling sunburn) and LFT abnormalities

Questions

What is a measure of a drug's affinity for a receptor?

> Ki - determined experimentally and is a measure of the affinity for a drug for a receptor (a measure of strength of the drug-receptor interaction)

The lower the Ki value, the _____ (*lower or higher*) the affinity of the antagonist for the receptor.

> Higher - On Exam: Ki values will be provided and we'll need to be able to determine the affinity of the antagonist for the receptor

Haloperidol

Prototypic high-potency antipsychotic agent

High affinity for D2 receptors

Side Effects: EPS and hyperprolactinemia

1st Gen (Typical) Antipsychotics

30 to 50% of SZ pt's do **NOT** respond to these drugs

Typical antipsychotic drugs improve positive sx, but only marginally improve negative sx and cognitive impairments of Sz

High incidence of ADRs

2nd gen (atypical) antipsychotics have been increasingly replacing them as the 1st-line tx of SZ

2nd Gen (Atypical) Antipsychotics

Clozapine, Olanzapine, Risperidone, Paliperidone, Ziprasidone, Quetiapine, Iloperidone, Asenapine, Lurasidone

Aripiprazole, Braxpiprazole, Cariprazine (*Considered 3rd gen*)

More effective than 1st gens in treating negative symptoms and improving cognitive functioning

Currently 1st line (except clozapine) due to fewer side effects than typical agents

Atypicals have also been associated with a reduction in the incidence of **suicide** in SZ

There is no uniform definition of the term "*atypical*" antipsychotic. They are a group of drugs that have at least equal antipsychotic efficacy compared to 1st gen *without* producing EPS and increased prolactin levels

MOA of 2nd Gens (Atypical)

Block 5-HT 2A receptors (*functionally, they are 5-HT-2A antagonists*)

Also block D2 receptors ⇨ D2 antagonism is still required to achieve antipsychotic effects

Also block other receptors (*H1, M1, alpha-1) ⇨ Side effects

Ziprasidone also inhibits 5-HT and NE uptake

1st Generation (Typical) Antipsychotic Drugs

Chemistry	Structure-Fxn relationships that were relied upon in the past have become less important
	Instead, receptor-fxn relationships and functional assays are more clinically relevant

1st Generation (Typical) Antipsychotic Drugs (cont)	
❃ Classification According to Potency ❃	
Low Potency	Chlorpromazine
	Thioridazine
Medium Potency	Loxapine
	Perphenazine
High Potency	**Haloperidol**
	Droperidol
	Fluphenazine
	Pimozide
❃ MOA ❃	
Block dopamine D2 receptors	D2 receptor binding affinity (but not D1) strongly correlates with clinical potency of typical antipsychotic agents
Blockade of postsynaptic D2 receptors	⇨ Reduction of dopaminergic neurotransmission
D2 receptor blockade in ALL dopaminergic pathways	⇨ beneficial in the mesolimbic pathway
	⇨ alleviates positive sx of SZ
	⇨ It doesn't do really anything for the negative or cognitive sx
	Side Effects:
	• D2 receptor blockade in nigrostriatal pathway ⇨ **extrapyramidal sx (EPS)**
	• D2 receptor blockade in the tuberoinfundibular pathway ⇨ **increased prolactin release** from the **anterior pituitary**
Blocks other receptors:	
5-HT2A blockade	Contributes to antipsychotic effects
Other receptor blockade	Numerous additional side effect
❃ SIDE EFFECTS ❃	

1st Generation (Typical) Antipsychotic Drugs (cont)	
EPS	Various movement disorders associated with antipsychotic therapy (occurs mostly with 1st gen)
	Occurs due to D2 receptor blockade in the nigrostriatal pathway
	• Akathisia: uncontrollable motor restlessness
	• Dystonias: muscular spasms of the neck, eyes, and tongue
	• Drug-Induced Parkinson's Syndrome: Resembles Parkinson's Syndrome
	• Tardive Dyskinesia (TD): occurs after months or years of tx; may become **irreversible**; repetitive, involuntary, purposeless movements (typically facial muscles are involved); **mechanism**: up-regulation and supersensitivity of D2 receptors (that can become permanent)
Hyperprolactinemia	D2 receptor blockade in the tuberoinfundibular pathway causes increased plasma prolactin levels (*Hyperprolactinemia*)
	Manifested as: Amenorrhea-galactorrhea in women, gynecomastia in men, Infertility in both men and women
ADRs caused by Blockade of Non-Dopamine Receptors	1st generation antipsychotic drugs also block 5-HT-2, alpha 1 adrenergic, muscarinic, and histamine H-1 receptors ⇨ More Side Effects
Blockade of H1 Receptors	Sedation

1st Generation (Typical) Antipsychotic Drugs (cont)	
Blockade of alpha 1 adrenergic receptors	Orthostatic hypotension (could result in falls and injuries)
Blockade of muscarinic receptors	dry mouth, urinary retention, blurred vision, tachycardia, constipation, toxic-confusional state
Blockade of both H1 and 5-HT-2A receptors	Weight gain
ADDITIONAL SIDE EFFECTS	
Typical antipsychotic agents affect hypothalamic function	impaired ability to regulate body temperature
	Hypo or Hyperthermia may result, depending on the ambient temperature
Thioridazine	Cardiac toxicity: reflected in prolongation of QTc interval and abnormal configuration of ST segment and T wave (correlates to increased risk of ventricular arrhythmias)
	Retinal Tox: (pigmentary retinopathy): decreased vision and "browining" of vision
Neuroleptic Malignant Syndrome (NMS)	Rare, but life-threatening reaction to antipsychotic drugs
	Symptoms: extreme muscle rigidity (lead pipe), hyperreflecia, fever, unstable BP, tachycardia, sweating, rapid changes in mental status, confusion, and coma
	Lab: myoglobinemia and metabolic acidosis