Antipsychotic Drugs

Main action: block DA receptors

Dopamine pathways

Mesolimbic	**Reward center, pos symptoms**	**Schizophrenia's pos sx due to too excess DA**
Mesocortical	Emotion/reasoning, neg symptoms	Schizophrenia's neg sx due to DA deficiency
Nigrostriatal	Parkinson's disease, movement	Side effects
Tuberoinfundibular	Pituitary hormones, ↑prolactin	

Dopamine receptor subtypes

D1 family	D1 receptors	Blocked by phenothiazines not butyrophenones, post-synaptic
	D5 receptors	Frontal cortex, limbic system
D2 family	D2 receptors	Blocked by all AP, post-synaptic
	D3 receptors	Blocked by most AP, limbic system
	D4 receptors	Frontal cortex, amygdala, clozapine has high affinity
DA Autoreceptor		Pre-synaptic Agonists ↓DA release, antagonists ↑DA release

History

- 1st phenalthiazine: chlorpromazine
- 1st butyrophenone: haloperidol
- 1st serotonin dopamine antagonist: risperidone

Classification

- **Typical antipsychotics** (1st generation) – 9
  - M1, H1, α1, D2
  - Phenothiazines: chlorpromazine, thioridazine, trifluoperaizine, fluphenazine
  - Thioxanthenes: thiothixene
  - Butyrophonenones: haloperidol
    - α1, D2
  - Others: molindone, loxapine, reserpine
- **Atypical antipsychotics** (2nd generation) – 10
  - Mixed antagonists: clozapine, olanzapine, quetiapine
    - Blocks everything, lot of different receptor actions
  - Serotonin dopamine antagonists (SDA): risperidone, paliperidone, ziprasidone, iloperidone, asenapine
    - 5-HT2A > D2
    - Risperidone also has α1
  - Dopamine partial agonist/5-HT2A antagonist: aripiprazole

Choosing an antipsychotic:

Atypical $\xrightarrow{6\ weeks}$ another atypical or typical $\xrightarrow{Last\ resort}$ Clozapine

Therapeutic trials: usually 6 weeks, clonidine is 12 weeks

Looooooong acting formulations

- Haloperidol decanoate 4 weeks
- Fluphenazine decanoate 2-4 weeks
- Risperidone long acting 2 weeks
- Paliperidone palmitate 4 weeks
- Olanzapine palmoate 2-4 weeks
- ***Need to determine tolerability with po first***

Antipsychotic effects

- Delayed onset of action (most): 2-6 weeks → need 6 week trial
- Clozapine onset of action: 12 weeks → need 12 week trial
- Prevention of relapse: 25% relapse rate → but can't give AP forever due to SE
- Neurotransmitter action
    - Mesolimbic: block only DA: ↓positive symptoms, but may ↑negative symptoms
    - Mesocortical: block 5-HT to ↑DA: ↓negative symptoms
        - Typicals: only block DA (action on mesolimbic only)
        - Atypicals: block by DA and 5-HT (action on both mesolimbic & mesocortical)

Adverse effects

- **Black box warning:** elderly with delirium + antipsychotic → ↑death
- **Extrapyramidal side effects (EPS):** anti-dopaminergic effects
    - Presentation: similar to Parkinson's disease
    - Mechanism: blocked D2 receptors in nigrostriatal pathway
    - Modulated by ACh and 5-HT
        - Inverse relationships: ↑5HT = ↓DA = ↑ACh (therefore, SSRIs can cause EPS)
        - Anti-ACh ↓EPS: many AP already have anti-ACh action, or add centrally-acting antimuscarinics (benztropine, trihexyphenidyl)
        - Anti-5HT ↓EPS
        - Typicals have ↑EPS because ↑D2 antagonism but no 5HT2A antagonism and no anti-ACh properties
    - Early onset (≤4 weeks): akathisia, dystonic reactions, pseudoparkinsonism
        - Akathisia
            - Onset: usually within 1-4 weeks
            - Risk factors: 30-60 y/o, female, high potency typical
            - Tx: ↓dose, propranolol, BZDs, anticholinergics, switch agent
        - Dystonic reactions
            - Onset: usually within 4 days
            - Risk factors: <40 y/o, male, high dose, high potency typical
            - Tx: stop agent or 3 Ben's: anticholinergic (benztropine, Benadryl), BZD (lorazepam)
        - Pseudoparkinsonism
            - Onset: usually about 4 weeks or more
            - Risk factors: elderly, female, high potency typical
            - Tx: ↓dose, switch agents, anticholinergic
    - Late onset: tardive dyskinesia
        - Long term D2 blockade → D2 receptor hypersensitivity → up-regulation (↑D2 receptors)
        - Onset: 6 months or later
        - Risk factors: elderly, female, high potency typical
        - Cannot just stop AP: may worsen TD due to naked receptors from up-regulation
    - Highest offenders: haloperidol, perphenazine
- **Antimuscarinic effects**
    - Action: parasympathetic
    - Effects: constipation, blurry vision, dry mouth, drowsiness
    - Highest offenders: chlorpromazine, clozapine
- **Antiadrenergic effects**
    - Action: sympatholytic, block α1-NE receptors
    - Effects: hypotension, dizziness, drowsiness
    - Highest offenders: chlorpromazine, clozapine, iloperidone
- **Antihistaminic effects**
    - Action: block H1 receptors
    - Effects: weight gain, sedation

    - Highest offenders: clozapine > olanzapine > quetiapine > risperidone
- **Tuberoinfundibular effects**
    - Action: D2 blockade in tuberoinfundibular pathway
    - Effects: ↑prolactin release from anterior pituitary → hyperprolactinemia (women) + gynecomastia (men)
    - Highest offenders: haloperidol, perphenazine, risperidone, paliperidone
- **SE with unknown receptor mediation**
    - Agranulocytosis: clozapine
    - ↓Seizure threshold: all AP, clozapine especially
- **QT_C prolongation**
    - Block K+ channels → ↑risk of ventricular fibrillation, torsades de pointes, sudden cardiac death
    - Change in heart's membrane repolarization → >60 msec prolongation or total elevation >500 msec
    - Highest offenders: thioridazine, ziprasidone
    - Lower risk: lurasidone, haloperidol, asenapine
- **Typical antipsychotics adverse effects**
    - Low potency: chlorpromazine
        - High risk of sedation, anticholinergic effects, orthostasis
    - High potency: haloperidol, fluphenazine
        - High EPS
    - Thioridazine: pigmentary retinopathy
    - Phenothiazines: photosensitivity reactions

Antipsychotic agent profiles

Aripiprazole (Abilify)

- Indications: schizophrenia, bipolar disorder, adjunct treatment for depression, irritability in autism
- Actions
    - Partial D2 agonist
    - Partial 5HT1A agonist
    - Full 5HT2A antagonist
- Partial agonists
    - Normal concentrations: act as agonist
    - High concentrations: act as antagonists
- Adverse effects: nausea, somnolence, EPS, akathisia

Clozapine (Clozaril)

- Only antipsychotic shown to ↓suicidal ideation, and only antipsychotic indicated for refractory schizophrenia, greatest improvement for negative symptoms, superior to all other antipsychotics in success rate
- Therapeutic trial: 12 weeks
- Interactions: smoking ↑clearance & ↓efficacy (by 50%), also CYP1A2, 2C19, 2C9, 3A4
- Adverse effects: sedation, weight gain, hypersalivation, tachycardia, orthostatic hypotension, constipation
- Black box warning: seizures, leukopenia, neutropenia, agranulocytosis, myocarditis, cardiomyopathy
    - Special monitoring: weekly blood (WBC/ANC) for 6 months, then ever 2 weeks for 6 months, then every 28 days if WBC > 3500 or ANC > 2000
    - Symptoms to note: infection, lethargy, weakness, fever, sore throat

Olanzapine (Zyprexa)

- Indications: schizophrenia, bipolar disorder
- Side effects: somnolence, weight gain, asthenia, dry mouth, hyperlipidemia, hyperglycemia
- Long acting: requires registration, 3 hr monitoring
- Interactions: smoking induces CYP1A2 → ↑clearance & ↓efficacy

Quetiapine (Seroquel)

- Indications: schizophrenia, bipolar I disorder
- Side effects: somnolence, dizziness, weight gain

Risperidone (Risperdal)

- Indications: schizophrenia, bipolar mania, irritability in autism
- Side effects: anxiety, somnolence, parkinsonism, dizziness, greatest prolactin elevation

Ziprasidone (Geodon)

- Indications: schizophrenia, bipolar disorder
- Side effects: somnolence, non-akathisia EPS, nausea, akathisia, QT_C prolongation (black box warning)
- Must take with food (>350 kcal) for ↑absorption

Asenapine (Saphris)

- Indications: schizophrenia, bipolar I disorder
- Side effects: akathisia, other EPS, somnolence
- Formulation: sublingual tablets only → don't chew, avoid eating/drink 10 min after taking

Iloperidone (Fanapt)

- Indication: schizophrenia
- Side effects: dizziness, somnolence, tachycardia, nausea, dry mouth
- Starter pack: slow titration due to NE-α1 antagonism: dizziness, tachycardia, QT_C prolongation

Lurasidone (Latuda)

- Indication: schizophrenia
- Side effects: somnolence, any EPS, nausea
- Must take with food for ↑absorption

Paliperidone (Invega, Sustenna)

- Indications: schizophrenia, bipolar I disorder
- Side effects: non-akathisia EPS, somnolence, highest prolactin elevation (along with risperidone)
- Active metabolite of risperidone, not metabolized by CYPs