ANTIPSYCHOTIC DRUGS
Drugs and textbook reference

- Goodman & Gilman, 11th Edition, Chapter 18, pp 461-480
- Haloperidol
- Quetiapine
- Risperidone
- Aripiprazole
Psychosis is Disorganized or Irrational Behavior

A state of altered salience

Probably a heterogenous group of syndromes
Positive Symptoms of Psychosis

- Bizarre, overdone behavior
- Delusions and ideas of reference
- Hallucinations
- Hostility
- Hyperactivity
Negative Symptoms of Psychosis

- Blunted affect
- Poverty of speech
- Diminished sense of purpose
- Diminished social drive
Cognitive Deficits

- Impairments in:
  - Attention
  - Memory
  - Executive function (ability to plan, initiate and regulate goal-directed behavior)
Early treatments of psychosis

Bethlehem Asylum 'Bedlam', one of the first asylums (1403) Courtesy of the National Library of Medicine.

18th century asylum
Early treatment of psychosis

- Reserpine
- Insulin shock
- Ice or fever therapy
- Lobotomies
- Chlorpromazine
- Haloperidol

Consequence of antipsychotic drug discovery
DA Receptors are G-protein coupled metabotropic receptors

D1 receptor family
D1 & D5

↑ cAMP

D2 receptor family
D2, D3, D4

↓ cAMP
The potency of APD binding to DA D2 Receptors is $\propto$ to potency of clinical dose

Nestler et al., Molecular Neuropharmacology, c2001, p. 402
Pharmacological evidence supporting excess DA in the positive symptoms

- **Increasing dopamine worsens psychosis**
  - Amphetamine and cocaine
- **Decreasing dopamine ameliorates psychosis**
  - Blockade of DA receptors or DA synthesis
DA Neuroanatomy in Psychosis

- Prefrontal cortex
- Head of caudate nucleus
- Nucleus accumbens
- Amygdala
- Hypothalamus
- Thalamus
- Putamen
- Ventral tegmental area
- Substantia nigra
- Pituitary

Legend:
- Red: Mesocortical pathway
- Green: Mesolimbic pathway
- Blue: Nigrostriatal pathway
Model of DAergic activity in schizophrenia

Characteristics of Antipsychotic Drugs

- Active against psychosis of any origin: idiopathic, metabolic, drug-induced
- More active against ‘positive’ symptoms
- Antipsychotic drugs interfere with dopamine transmission, most block dopamine receptors
- Drugs start to work relatively quickly, but it takes a few months to reach maximum effect
Modern Course of Treatment

- New ‘atypical’ antipsychotic drugs (second generation)
- Conventional old-line drugs (first generation)
- Clozapine
First Generation Antipsychotic Drugs

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<thead>
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<th>Compound</th>
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Second generation antipsychotic drugs

- Risperidone (Risperdal)
- Olanzapine (Zyprexa)
- Ziprasidone (Geodon)
- Aripiprazole (Abilify)
- Quetiapine (Seroquel)
- Iloperadine (Fanapt)
Top selling drugs: 2010

## Second Generation Antipsychotic Drugs

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**Notes**
- **Risperidone** (*Risperdal*): Low D$_2$R specificity
- **Clozapine** (*Clozaril*): Low D$_2$R specificity
- **Olanzapine** (*Zyprexa*): Low D$_2$R specificity
- **Quetiapine** (*Seroquel*): Low D$_2$R specificity
- **Aripiprazole** (*Abilify*): [High] D$_2$R specificity
The action of aripiprazole, a D2R partial agonist will depend on intrinsic activity at dopaminergic synapse

Strange, TIPS, 29: 314, 2008
Absorption, Distribution and Fate of Antipsychotic drugs

- Erratic absorption
- Highly lipophilic
- \( t_{1/2} = 6-40 \) hrs, most taken once a day
- Metabolized by cytochrome P450 enzymes
- Clearance from brain may be slower than clearance from plasma
Depot forms of antipsychotic drugs

- Are depot forms for non-compliant patients
- Less plasma level drug fluctuation
- Lower relapse rates
- Poor patient acceptance and no flexibility in dosing
- Paliperidone ER (Invega, active metabolite of risperidone) uses oral osmotic pump extended release technology
## Actions of DA in dopaminergic pathways

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<thead>
<tr>
<th>CNS area</th>
<th>Effect of DA</th>
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<td>Mesolimbic area</td>
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<td>Cognition</td>
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<tr>
<td>Nigrostriatal pathway</td>
<td>Movement</td>
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<td>Tuberoinfundibular</td>
<td>Inhibit prolactin release</td>
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**Actions of Antipsychotic drugs in dopaminergic pathways**

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<td>Mesolimbic area</td>
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<td>Minimal effect on cognition</td>
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*In vitro* profiles of the relative ability of APDs to bind to specific receptors

Nestler et al., Molecular Neuropharmacology, c2001, p. 405
Other Actions of Antipsychotic drugs

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<tr>
<th>Area</th>
<th>Receptor blockade</th>
<th>Effect of APD</th>
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<tbody>
<tr>
<td>Autonomic effects</td>
<td>α-adrenergic, mACh, H1 histamine, serotonin Rs, esp. 5-HT1 and 5-HT2</td>
<td>Hypotension, ↓ ejaculation, dry mouth, sedation</td>
</tr>
<tr>
<td>Metabolic effects</td>
<td>Same as above &amp; D2Rs</td>
<td>Diabetes, weight gain</td>
</tr>
<tr>
<td>Cardiovascular effects</td>
<td>Direct and indirect effects</td>
<td>Mild orthostatic hypotension, prolongation QT interval (rare)</td>
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# First Generation Antipsychotic Drugs

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<th>Compound</th>
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<th>Motor (EP) Effects</th>
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Extrapyramidal (motor) side effects

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<tr>
<th>Effect</th>
<th>Time of Risk</th>
<th>Feature</th>
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<tr>
<td>Acute dystonia</td>
<td>1-5 days</td>
<td>Spasm of muscles, face, tongue, neck</td>
</tr>
<tr>
<td>Akathisia</td>
<td>5-60 days</td>
<td>Restlessness</td>
</tr>
<tr>
<td>Parkinsonism</td>
<td>5-30 days</td>
<td>Bradykinesia</td>
</tr>
<tr>
<td>Tardive dyskinesia</td>
<td>Months or years, seen when withdraw or lower dose of drug</td>
<td>Stereotyped or choreic movements of face, tongue, trunk</td>
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SGAs have separated dose response curves for efficacy and extrapyramidal symptoms

Casey, J. Clinical Psych., 58:Suppl. 10, 55, 1997
Factors that may play a role in reduced EPS of 2nd generation drugs

- **Receptor occupancy?**
  - ~50-60% of D2Rs need to be occupied to get therapeutic effect
  - ≥ 80% occupation gives EPS
  - Aripiprazole occupies ~85%

- **Receptor binding profile:** most SGAs have high affinity for a number of serotonin receptor subtypes
Tolerance and dependence to antipsychotic drugs

- Not addicting
- Relapse in psychosis if discontinued abruptly

- Tolerance develops to sedative effects
- No tolerance to prolactin secretion
- No tolerance to antipsychotic effect
Drug Interactions of Antipsychotic drugs

- CNS Depressants: will potentiate actions of other CNS depressants
- Blocks effects of l-dopa and dopaminergic agonists
- Most are metabolized by P450 system, will be affected by drugs that alter P450
DA-Glutamate model of schizophrenia

- ↑ limbic DAergic activity
- ↓ prefrontal ctx DAergic activity
- ↓ glutamatergic input into limbic region and DA cell bodies

NMDA Hypothesis of Schizophrenia

- Reducing glutamate worsens psychotic symptoms
- NMDA agonists improve symptoms in schizophrenia
N-methyl-D-aspartate receptor ligands

- Agonist: glutamate
- Co-agonist: glycine or D-serine
- Permeability: Ca\(^{2+}\) and Na\(^{+}\)
- Phencyclidine (PCP) and ketamine: noncompetitive antagonists

Meyer & Quenzer, Psychopharmacology, c2005, p. 168
Upcoming therapies for schizophrenia

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<th>Therapy</th>
<th>Effect</th>
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<tr>
<td>Glycine, sarcosine, D-serine</td>
<td>Enhance NMDA activity, reduce negative symptoms, cognitive enhancement</td>
</tr>
<tr>
<td>Glutamate reuptake inhibitors</td>
<td>Increase synaptic glutamate</td>
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<tr>
<td>DA D1 receptor agonist</td>
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