Psychoses and Antipsychotics: A burden of riches

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Objectives

- Recognize the characteristics of psychosis
- Explain the primary mechanism of action of antipsychotic agents
- Describe the mechanisms leading to toxic motor side effects
- Discuss the differences in induction of motor side effects by older and newer agents
- List the various side effects associated with both older and newer agents
- Explain the links between the multitude of receptors targeted by antipsychotic agents and different side effects associated with different agents
Psychoses v. Neuroses

- **Psychoses**
  - Mental disorders characterized by rifts in rational thought, inappropriate processing of sensory information, and disturbed views of reality and self. Psychotic symptoms are generally not recognized as such by the sufferer.

- **Neuroses**
  - Abnormal reaction to an external state that is generally recognized as abnormal by the sufferer.

Psychotic markers

- Delusions and/or paranoia
- Hallucinations
  - Auditory most common
- Disordered thoughts/Loose ideation
- Flat affect/anhedonia
Psychoses in disease states

- Delirium in dementia
- Manic psychoses
- Secondary to severe depression
- Post-traumatic stress disorders
- Drug-induced
  - Amphetamine, steroid, LSD, ketamine, etc.
- Schizophrenia-multiple subtypes

Disease statistics for schizophrenia

- ~1% of the population in the U.S.
- Men and women equally affected
- Age of onset from 15-25 years
- High mortality rate (10%), poor longterm prognosis
Etiology of schizophrenia

- Genetic and environmental factors
  - Predisposition from twin studies
  - Perinatal insults increase incidence
- Anatomic irregularites
  - Enlarged cerebral ventricles
  - Reduced cortical mass

Monozygotic twins

Unaffected  Schizophrenic

Functional irregularities

- Reduced prefrontal cortex activity
- Poor visual tracking
Treatment Options

- Frontal Lobotomy
  - Used extensively in 1940s and 50s
  - Calmed patients
  - Permanently debilitating
- Psychotherapy
  - Ineffective
- Behavioral therapy
  - Improve social skills
  - Improve life skills, e.g., job attendance, housing
  - Personal hygiene
- Nicotine??

Antipsychotic agents

- Most effective means of treating overt symptoms of psychosis
- Neuroleptics, antischizophrenics, or major tranquilizers
- Effective in 70% of psychotic patients
  - Used chronically to prevent relapse (90% vs 10 to 50% relapse rate with treatment
- NOT anesthetics
Latency of effectiveness

– Calming (tranquilizing) effects may be seen within minutes to hours
– Diminished psychotic symptoms within 24-28 hours.
– Full antipsychotic effects evolve over 2-6 weeks.
– Improvement may continue for up to 6 months

Dopamine hypothesis of schizophrenia

- Antipsychotic affinity for “D2”-like receptors correlates with average clinical dose (a measure of potency?)

From P. Seeman, Synapse 1:133 (1987)
Antipsychotic Pharmacology
– ALL are D2 antagonists or weak partial agonists

What are the important downstream effectors?

Dopaminergic pathways

• Mesolimbic
  – VTA to nucleus accumbens, amygdala, and olfactory tubercle

• Mesocortical
  – VTA to frontal, prefrontal cortices

Sites of dysfunction in schizophrenia?
Dopaminergic pathways

- **Tuberoinfundibular pathway**
  - Hypothalamus to pituitary
  - D2 receptors inhibit prolactin release from lactotrophs

- **Nigrostriatal pathway**
  - Initiation of movement and control of muscle tone
  - Selectively degenerated in Parkinson's disease
  - Involved in obsessive/compulsive disorders
  - Antagonism of D2 receptors produces extrapyramidal side effects (EPS)
"Rich" pharmacology

Table 22.2. The receptor affinity values of new and traditional antipsychotic drugs for a group of common CNS neurotransmitter receptors. Whereas, some drugs have restricted affinities (e.g., haloperidol), others like clozapine have very broad affinity profiles.

<table>
<thead>
<tr>
<th>Receptor</th>
<th>Haloperidol</th>
<th>Clozapine</th>
<th>Olanzapine</th>
<th>Seroquel</th>
<th>Risperidone</th>
<th>Ziprasidone</th>
</tr>
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<tbody>
<tr>
<td>D1</td>
<td>210</td>
<td>85</td>
<td>31</td>
<td>460</td>
<td>430</td>
<td>525</td>
</tr>
<tr>
<td>D2</td>
<td>1</td>
<td>160</td>
<td>44</td>
<td>580</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>D3</td>
<td>2</td>
<td>170</td>
<td>50</td>
<td>940</td>
<td>10</td>
<td>7</td>
</tr>
<tr>
<td>D4</td>
<td>3</td>
<td>50</td>
<td>50</td>
<td>1,900</td>
<td>10</td>
<td>32</td>
</tr>
<tr>
<td>SHT2A</td>
<td>45</td>
<td>16</td>
<td>50</td>
<td>300</td>
<td>0.5</td>
<td>0.4</td>
</tr>
<tr>
<td>SHT1A</td>
<td>1,100</td>
<td>200</td>
<td>&gt;10,000</td>
<td>720</td>
<td>210</td>
<td>3</td>
</tr>
<tr>
<td>SHT2C</td>
<td>&gt;10,000</td>
<td>10</td>
<td>11</td>
<td>5,100</td>
<td>25</td>
<td>1</td>
</tr>
<tr>
<td>SHT1D</td>
<td>&gt;10,000</td>
<td>1,900</td>
<td>800</td>
<td>6,200</td>
<td>170</td>
<td>2</td>
</tr>
<tr>
<td>NE uptake</td>
<td>1,700</td>
<td>5,000</td>
<td>ND</td>
<td>ND</td>
<td>1,300</td>
<td>50</td>
</tr>
<tr>
<td>5HT reuptake</td>
<td>4,700</td>
<td>500</td>
<td>ND</td>
<td>ND</td>
<td>&gt;10,000</td>
<td>50</td>
</tr>
<tr>
<td>a1</td>
<td>6</td>
<td>19</td>
<td>11</td>
<td>14</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>a2</td>
<td>360</td>
<td>8</td>
<td>230</td>
<td>90</td>
<td>1</td>
<td>200</td>
</tr>
<tr>
<td>H1</td>
<td>440</td>
<td>1</td>
<td>3</td>
<td>11</td>
<td>20</td>
<td>50</td>
</tr>
<tr>
<td>5HT6</td>
<td>9,600</td>
<td>14</td>
<td>10</td>
<td>33</td>
<td>2,200</td>
<td>130</td>
</tr>
<tr>
<td>5HT7</td>
<td>1,200</td>
<td>100</td>
<td>150</td>
<td>130</td>
<td>2</td>
<td>23</td>
</tr>
<tr>
<td>Muscarinic</td>
<td>5,500</td>
<td>2</td>
<td>2</td>
<td>&gt;1,000</td>
<td>&gt;1,000</td>
<td>&gt;1,000</td>
</tr>
</tbody>
</table>

The data in this table were by Dr. Robert A. Lubs.

Table from Neurobiology of Mental Illness. Chpt. 22, Principles of the pharmacotherapy of schizophrenia by Carol A. Tamminga

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Common typical neuroleptics

- Phenothiazines and related thioxanthines
  - Chlorpromazine (Thorazine®), the grandparent of all antipsychotics
  - Thioridazine (Mellaril®), Fluphenazine (Prolixin®), Thiothixene (Navane®)

- Butyrophenones and related compounds
  - More D2 selective
  - Haloperidol (Haldol®), Droperidol, Pimozide (Orap®)
Common atypical neuroleptics

– Dibenzazepines and related
  Clozapine (Clozaril®), Loxapine (Loxitane®),
  Olanzapine (Zyprexa®), Quetiapine (Seroquel®)
– Others
  Risperidone (Risperdal®), Ziprasidone (Geodon®),
  Molindone (Moban®), Aripiprazole (Abilify®)

Toxic dose-limiting effects:
Extrapyramidal side effects (EPS) /Acute dyskinesias

• Akathisia
  – Motor restlessness and distress compels constant movement

• Dystonia
  – Spasms of neck and face muscles including grimacing, torticollus,
    ocular dysfunction
  – Involuntary, frequently painful movements and bodily distortions

• Respiratory distress
  – Pharyngeal /Laryngeal dysfunction

• Parkinsonian syndrome
  – Bradykinesia and rigidity
  – Resting tremor of head and hands
  – Flat affect
EPS

- Dose Related—Most common with high dose bolus or initial depo injection
- Treat by decreasing dose, changing drugs, adding anti-Parkinson agents
- Women are more sensitive than men
- Lead to irreversible tardive dyskinesias
- Less selective antipsychotics (the dirty drugs) cause fewer EPS

Muscarinic receptor affinity is inversely correlated with EPS

<table>
<thead>
<tr>
<th>Drug</th>
<th>Kd (nM)</th>
<th>Frequency of EPS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thioridazine</td>
<td>10</td>
<td>+</td>
</tr>
<tr>
<td>Clozapine</td>
<td>7.5</td>
<td>+</td>
</tr>
<tr>
<td>Chlorpromazine</td>
<td>60</td>
<td>++</td>
</tr>
<tr>
<td>Promazine</td>
<td>160</td>
<td>++</td>
</tr>
<tr>
<td>Thiothixene</td>
<td>2500</td>
<td>+++</td>
</tr>
<tr>
<td>Fluphenazine</td>
<td>2000</td>
<td>++++</td>
</tr>
<tr>
<td>Haloperidol</td>
<td>&gt;5000</td>
<td>++++</td>
</tr>
</tbody>
</table>

Data compiled from Goodman and Gilman's (2001)
Motor output disturbances

Muscarinic antagonists help to reset the motor output imbalance caused by D2 antagonists

Tardive dyskinesias

Occurs in 50% of patients treated with antipsychotics
Severity is related to dose, duration of treatment, and gender

Tardive dyskinesias/tardive psychosis

Atypical Antipsychotics

- Lowered incidence of EPS
- Somewhat lower affinity for D2 dopamine receptors (5-50X)
- Affinity for 5-HT2 receptors
- Recommended as first line therapies
  - Higher costs
- Side effects vary based on pharmacologic profile

<table>
<thead>
<tr>
<th>Drug</th>
<th>5HT2A/D2 affinity ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thioridazine</td>
<td>17.8</td>
</tr>
<tr>
<td>Fluphenazine</td>
<td>23.8</td>
</tr>
<tr>
<td>Haloperidol</td>
<td>9.00</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>1.84</td>
</tr>
<tr>
<td>Ziprasidone</td>
<td>0.09</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>0.36</td>
</tr>
<tr>
<td>Chlorpromazine</td>
<td>0.07</td>
</tr>
<tr>
<td>Risperidone</td>
<td>0.05</td>
</tr>
<tr>
<td>Clozapine</td>
<td>0.01</td>
</tr>
</tbody>
</table>
Serotonergic CNS pathways

- Projections from the raphé to the pre-frontal cortex, hypothalamus, limbic areas, spinal reflex areas, and basal ganglia

Fewer EPS with 5-HT₂ antagonist / lower affinity D2 antagonist antipsychotics
## Adverse effects profiles

<table>
<thead>
<tr>
<th>Drug</th>
<th>Sedation</th>
<th>EPS</th>
<th>Hypotension</th>
<th>Anticholinergic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chlorpromazine</td>
<td>+++</td>
<td>++</td>
<td>+++</td>
<td>++</td>
</tr>
<tr>
<td>Thioridazine</td>
<td>+++</td>
<td>+</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>Fluphenazine</td>
<td>+</td>
<td>++++</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Haloperidol</td>
<td>+</td>
<td>++++</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Thiothixene</td>
<td>+</td>
<td>+++</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Clozapine</td>
<td>+++</td>
<td>0</td>
<td>+++</td>
<td>++*</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>+</td>
<td>+</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>+++</td>
<td>0</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Risperidone</td>
<td>+</td>
<td>++*</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Ziprasidone</td>
<td>+</td>
<td>++</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Aripiprazole</td>
<td>+</td>
<td>+</td>
<td>++</td>
<td>+</td>
</tr>
</tbody>
</table>

Data compiled from Goodman and Gilman’s and Neurobiology of Mental Illness

## Autonomic effects

- **α1 adrenergic antagonism**
  - Increased appetite
  - Hypotension, esp. postural/dizziness
  - Reflex tachycardia
  - Urinary incontinence

- **Muscarinic cholinergic antagonism (Anticholinergic)**
  - Dry mouth, constipation, urinary retention
  - Blurred vision, increased intraocular pressure
  - Confusion and memory loss
  - Tachycardia
Sedation

• Histamine H1 antagonism
  – Drowsiness and sedation
  – Weight gain
  – Antinausea effects on the vestibular apparatus
• Difficult for patients on prophylactic or chronic therapy
• Very useful for acute treatment of florid psychoses with agitation

Endocrine effects

• D2 dopamine antagonism
• Attenuation of D2 inhibition of prolactin release at pituitary lactotrophs
  – Gynecomastia and increased lactation
  – Disturbed thermal regulation (hypo/hyperthermia)
  – Amenorrhea, infertility, and sexual dysfunction
• Prolactin levels > 100 → prolactinomas, ↑ risk of breast cancer
Hypersensitivity reactions

- Primarily with phenothiazines (5%)
  - Dermal reactions including rash photosensitivity
  - Ocular opacities of the cornea and lens
  - Jaundice

Weight gain/Metabolic disorder

Serotonin, H1 histamine and $\alpha_1$ adrenergic blockade?

- Increased appetite
- Increased fat storage
- Hypercholesterolemia
- Changes in glucose metabolism
- Hyperglycemia
- Sleep apnea

<table>
<thead>
<tr>
<th>Large weight gain (4-6 kg)</th>
<th>Clozapine, Olanzapine, Chlorpromazine, Thioridazine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moderate weight gain (1-3 kg)</td>
<td>Risperidone, Quetiapine, Sertindole</td>
</tr>
<tr>
<td>Weight neutral</td>
<td>Ziprasidone, Aripiprazole, Molindone, Haloperidol</td>
</tr>
</tbody>
</table>

Am. J. Psych. 156:1686
Potentially fatal cardiotoxicities

- Increased risk of sudden cardiac death
  - Muscarinic and $\alpha_1$ adrenergic antagonist activities
  - Weight gain and cardiovascular disease increase
  - Smoking
  - Prolonged QT interval may cause Torsades de pointe arrhythmias
    - E.g., pimozide, ziprasidone & thioridazine
    - Increase 5-20 msec on average, 60 msec increase is a high risk factor for Tdp
    - Inhibition of IR$_K$ channels?

FDA Public Health Advisory
April 2005

The Food and Drug Administration has determined that the treatment of behavioral disorders in elderly patients with dementia with atypical (second generation) antipsychotic medications is associated with increased mortality. Of a total of 17 placebo controlled trials performed with olanzapine (Zyprexa), aripiprazole (Abilify), risperidone (Risperdal), or quetiapine (Seroquel) in elderly demented patients with behavioral disorders, … a total of 5106 patients, … demonstrated an approximately 1.6-1.7 fold increase in mortality in these studies. Examination of the specific causes of these deaths revealed that most were either due to heart related events (e.g., heart failure, sudden death) or infections (mostly pneumonia).
Neuroleptic malignant syndrome

Rare, recurrent with 10% mortality rates
- Related to D2 antagonism?
- Manifestations
  - Hyperthermia and diaphoresis
  - Tremor and muscle rigidity
  - Altered mental status, including catatonia and stupor
  - Fluctuating blood pressure and pulse
  - Acute renal failure
- Treatment
  - Immediate discontinuation of all antipsychotic medication
  - Dantrolene may be helpful for unknown reasons
  - Bromocriptine, a dopamine agonist, may be helpful in large doses

Clozapine:
Unique efficacy and toxicities

- Significant Advantages
  - Uniquely effective in 25-30% of treatment-resistant patients
  - No reported EPS
- Life threatening toxicities
  - Leukopenia (3%) can lead to fatal agranulocytosis (1.3%)--weekly WBC monitoring for 6 mos, biweekly thereafter
  - Myocarditis
  - Cardiovascular collapse (hypotension, respiratory and/or cardiac arrest)
- Decreased seizure threshold
Other atypical agents

• Olanzapine (Zyprexa®)
  – Very similar in structure and profile but lacking the
    unique toxicities and efficacy of clozapine
  – Weight gain is problematic

• Risperidone (Risperdal®)
  – Can be agitating
  – Dose needs to be controlled to avoid EPS
  – Metabolized by Cyp2D6
    • Interactions with Cyp 2D6 inhibitors, e.g. Paxil, Prozac and
      Zoloft, increase Risperdal plasma concentrations up to 4X

• Ziprasidone (Geodon®)
  – Low weight gain, low EPS
  – Affinity for the NE transporter/Antidepressant?
  – Problems with QT elongation

• Quetiapine (Seroquel®)
  – No EPS, low autonomic effects, moderate weight gain
  – Sedating
Occupancy theory of antipsychotic propensity for EPS

Incidence of EPS may be related to “occupancy” of D2 receptors in the absence and presence of a spike of dopamine

Aripiprazole (Abilify®)

- Dopamine/Serotonin “system stabilizer
  - Efficacy comparable to Haldol
  - D2 partial agonist
    - Transient nausea
    - No endocrine disturbances
      - Slight decrease in prolactin
    - No receptor sensitization
      - Low risk for EPS or TD
  - 5HT₁A partial agonist, 5HT₂ antagonist, α₁A antagonist
  - May increase psychoses in some patients
  - Agitating
Additional indications

- **Neuroleptanesthesia**
  - Innovar® = Droperidol plus fentanyl

- **Tourette’s syndrome**
  - Uncontrolled vocal outbursts, tics and repetitive movements
  - Too much dopaminergic activity in the nigrostriatal pathway
  - Treat with a high affinity D2 antagonist, e.g., pimozide (Orap®)

- **Severe nausea and vomiting**
  - D2 antagonists block the CTZ and increase GI motility
  - Antihistamine and anticholinergic effects block motion sickness
  - Promethazine (Phenergan®) Prochlorperazine (Compazine®)

- **Intractable hiccups**
- **Insufficient lactation**
  - Inhibit D2 inhibition of prolactin release
  - Metoclopramide (Reglan®)

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**BIPOLAR DISORDER**

- Recurrent illness
- Cycles of depression and mania with a periodicity of days/weeks to months
  - Manic phase typically lasts one week but may be proceeded by weeks or months of hypomanic activity
  - Depressive phase may last much longer (several months) and is characterized by extreme inertia and apathy
  - Rapid cyclers are difficult to treat and stabilize
- Affects 1-2% of the U.S. adult population
- Men and women affected equally
- Onset from 18-45 yrs
- Has a genetic component
Symptoms of mania

– Persistently elevated mood and extreme extrovertedness
– Exaggerated sense of self-importance leading to delusions of grandeur
– Fearlessness, engagement in high-risk, thrilling behaviors (sky-diving)
– Poor impulse control (gambling, over-spending)
– Excessive libido
– Verborrhea (rapid and continuous speech),
– Racing thoughts and distractibility
– Hyperactivity, insomnia, irritability and impatience that can lead to paranoia

Mood Stabilizers

– Different treatments for simple depression and bipolar disorder
  • Antidepressant medications can precipitate a manic phase
– Lithium Carbonate
  • Inorganic cation, excreted in urine unmetabolized
  • Most effective treatment for bipolar disorder
    – Effective in 80% of manic attacks within 1-2 weeks
    – Problems with toxicity must be considered with need for efficacy
  • No effect in normal subjects
  • Used prophylactically to prevent mood swings and cycling into a manic phase
  • Mode of action is still poorly understood
Cellular effects of Li++

Adverse effects of Li++

- Lithium substitutes for Na+ and Mg++, but is less efficient
  - Accumulates in excitable cells and disrupts action potentials
  - Low therapeutic index (~2)

- Adverse effects that decrease over time
  - Nausea, vomiting
  - Muscle weakness and fatigue

- Persistent adverse effects
  - Hand tremors (sometimes very debilitating)
  - Polydipsia and polyuria
    - Maintain normal sodium intake as Na+ deficiency increases Li++ toxicity
    - Regulate H2O intake
    - Contraindicated with compromised renal function
Toxic effects of Li$^{++}$

- **Toxicity at slightly higher doses**
  - Ataxia and slurred speech
  - Confusion and disorientation
  - Hypotension
- **Overdose toxicities**
  - Seizure
  - Muscle rigidity, deep tremor
  - Cardiac arrhythmias
  - Coma and death

Anti-convulsant mood stabilizers

- Not as effective as lithium, but not as toxic
- Onset of action is much quicker than lithium
- Mode of action probably related to general CNS inhibition
- Problems may include weight gain, sleepiness, and inability to concentrate, diaphragmatic depression
Anti-convulsant mood stabilizers

- **Valproic acid, divalproex (Depakote®) and clonazepam**
- **Carbamazepine (Tegretol®), oxcarbazepine (Tripleptal®)**
  - Tricyclic compounds related to imipramine
- **Topiramate (Topamax®)**
  - Fewer problems with weight gain
  - May induce a rare type of closed angle glaucoma

Other treatments for mania

- **Antipsychotics**
  - Used as mood stabilizers
  - Dosage for treating bipolar disorder is often much less than for schizophrenia
  - Mode of action may be related to inhibition of serotonin receptors in combination with anti-histamine-related sedating effects
- **Benzodiazepine sedatives**
  - Rapid efficacy
  - Not a long term treatment option
- **Vitamin B12**
  - Consider supplementation with OCD
References