Antipsychotics

Dr. Nasser A. H. Al-Harchan
Asst. Prof. of Pharmacology
College of Medicine
Baghdad University
Schizophrenia

Etiology

- Exact etiology unknown
  - Genetic predisposition
  - Intrauterine, birth or postnatal complications
  - Viral CNS infections
  - Environmental stressors (biochemical or social)

- No evidence of association with poor parenting
Schizophrenia

- Pathophysiology
  - No consistent neuropathology or biomarkers for schizophrenia
    - Increased dopamine in mesolimbic pathways causes delusions and hallucinations
    - Dopamine deficiency in mesocortical and nigrostriatal pathways causes negative symptoms (apathy, withdrawal)
  - Halocinogens produce effect through action on 5-HT2 receptors
Schizophrenia

- Antipsychotics
  - Typical / Conventional antipsychotics
  - Atypical antipsychotics
Typical / conventional antipsychotics

<table>
<thead>
<tr>
<th>Track</th>
<th>Origin</th>
<th>Innervations</th>
<th>Function</th>
<th>Antipsychotic effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mesolimbic</td>
<td>Midbrain, Ventral tegmental</td>
<td>Limbic structure, nucleus accumbens</td>
<td>Emotional and intellectual</td>
<td>↓ Hallucinations, delusions, disordered cognition</td>
</tr>
<tr>
<td>Mesocortical</td>
<td>Ventral tegmental</td>
<td>Frontal cortex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nigrostriatal</td>
<td>Substantia nigra</td>
<td>Basal ganglia</td>
<td>Extrapyramidal system movement</td>
<td>↑ Motor symptomatology</td>
</tr>
<tr>
<td>Tubero-infundubular</td>
<td>Hypothalamus</td>
<td>Pituitary gland</td>
<td>Regulate endocrine functions</td>
<td>↑ Plasma prolactin levels</td>
</tr>
</tbody>
</table>
Typical / conventional antipsychotics

- **Mechanism of action**
  - Blocks receptors for dopamine, acetylcholine, histamine and norepinephrine
  - Current theory suggests dopamine2 (D2) receptors suppresses psychotic symptoms
    - All typical antipsychotics block D2 receptors
    - Close correlation between clinical potency and potency as D2 receptor antagonists
Typical / conventional antipsychotics

- Properties
  - Effective in reducing positive symptoms during acute episodes and in preventing their reoccurrence
  - Less effective in treating negative symptoms
    - Some concern that they may exacerbate negative symptoms by causing akinesia
  - Higher incidence of EPS / sedation / anticholinergic Adverse effects
Typical / conventional antipsychotics

- **Potency**
  - All have same ability to relieve symptoms of psychosis
  - Differ from one another in terms of potency
    - i.e. size of dose to achieve a given response
  - When administered in therapeutically equivalent doses, all drugs elicit equivalent antipsychotic response
Typical / conventional antipsychotics

- Low potency
  - Chlorpromazine, thioridazine

- Medium potency
  - Perphenazine

- High potency
  - Trifluoperazine, thiothixene, fluphenazine, haloperidol, pimozide
## Typical / conventional antipsychotics

<table>
<thead>
<tr>
<th>Potency</th>
<th>Drug</th>
<th>Equiv oral dose (mg)</th>
<th>EPS</th>
<th>Sedation</th>
<th>Anticholinergic s/e</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>Chlorpromazine</td>
<td>100</td>
<td>Moderate</td>
<td>High</td>
<td>Moderate</td>
</tr>
<tr>
<td></td>
<td>Pericyazine</td>
<td>NA</td>
<td>Low</td>
<td>High</td>
<td>Low</td>
</tr>
<tr>
<td></td>
<td>Thioridazine</td>
<td>100</td>
<td>Low</td>
<td>High</td>
<td>High</td>
</tr>
<tr>
<td>Moderate</td>
<td>Perphenazine</td>
<td>10</td>
<td>Moderate</td>
<td>Moderate</td>
<td>Low</td>
</tr>
<tr>
<td>High</td>
<td>Trifluoperazine</td>
<td>5</td>
<td>High</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td></td>
<td>Thiothixene</td>
<td>2</td>
<td>High</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td></td>
<td>Fluphenazine</td>
<td>2</td>
<td>High</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td></td>
<td>Haloperidol</td>
<td>2</td>
<td>High</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td></td>
<td>Pimozide</td>
<td>0.5</td>
<td>High</td>
<td>Moderate</td>
<td>Moderate</td>
</tr>
<tr>
<td></td>
<td>Sulpiride</td>
<td>200</td>
<td>Low</td>
<td>Moderate</td>
<td>Low</td>
</tr>
</tbody>
</table>
## Typical / conventional antipsychotics

<table>
<thead>
<tr>
<th>Drug</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chlorpromazine</td>
<td>Generic, inexpensive</td>
<td>Many adverse effects (esp. autonomic)</td>
</tr>
<tr>
<td>Thioridazine</td>
<td>Slight EPS, generic</td>
<td>Cardiotoxicity (QT prolongation)</td>
</tr>
<tr>
<td>Fluphenazine</td>
<td>Generic, depot available</td>
<td>(?) increased tardive dyskinesia</td>
</tr>
<tr>
<td>Thiothixene</td>
<td>(?) decreased tardive dyskinesia</td>
<td>Uncertain</td>
</tr>
<tr>
<td>Haloperidol</td>
<td>Generic, injection and depot A/V, few autonomic s/e</td>
<td>Prominent EPS</td>
</tr>
</tbody>
</table>
Typical / conventional antipsychotics

<table>
<thead>
<tr>
<th>Receptor type</th>
<th>Consequence of blockade</th>
</tr>
</thead>
<tbody>
<tr>
<td>D2 dopaminergic</td>
<td>Extrapyramidal symptoms; prolactin release</td>
</tr>
<tr>
<td>H1 histaminergic</td>
<td>Sedation</td>
</tr>
<tr>
<td>Muscarinic cholinergic</td>
<td>Dry mouth, blurred vision, urinary retention, constipation, tachycardia</td>
</tr>
<tr>
<td>Alpha1-adrenergic</td>
<td>Orthostatic hypotension; reflex tachycardia</td>
</tr>
<tr>
<td>5-HT2 serotonergic</td>
<td>Weight gain</td>
</tr>
</tbody>
</table>
Typical / conventional antipsychotics

- **Adverse effects**
  - **Extrapyramidal symptoms (EPS)**
    - Early reactions - can be managed with drugs
      - Acute dystonia
      - Parkinsonism
      - Akathisia
    - Late reaction - drug treatment unsatisfactory
      - Tardive dyskinesia (TD)
  - Early reactions occur less frequently with low potency drugs
  - Risk of TD is equal with all agents
Typical / conventional antipsychotics

- **Adverse effects**
  - **Acute dystonia**
    - Develops within a few hours to 5 days after first dose
    - Muscle spasm of tongue, face, neck and back
    - Oculogyric crisis (involuntary upward deviation of eyeballs)
    - Opisthotonus (tetanic spasm of back muscles, causing trunk to arch forward, while head and lower limbs are thrust backwards)
  - Laryngeal dystonia can impair respiration
- **Management**
  - Anticholinergics (Benztropine, diphenhydramine IM/IV)
  - Lower or split dosing
  - Switch agent
  - Add scheduled benztropine / diphenhydramine with antipsychotic
Typical / conventional antipsychotics

- **Adverse effects**
  - Parkinsonism (neuroleptic induced)
    - Occurs within first month of therapy
    - Bradykinesia, mask-like facies, drooling, tremor, rigidity, shuffling gait, cogwheeling, stooped posture
    - Shares same symptoms with Parkinson’s disease
  - Management
    - Centrally acting anticholinergics (scheduled benztropine / diphenhydramine / benzhexol with antipsychotics) and amantadine
    - Avoid levodopa as it may counteract antipsychotic effects
    - Switch to atypical antipsychotics for severe symptoms
Typical / conventional antipsychotics

- Adverse effects
  - Akathisia
    - Develop within first 2 months of therapy
    - Compulsive, restless movement
    - Symptoms of anxiety, agitation
  - Management
    - Beta blockers (propranolol)
    - Benzodiazepines (e.g. lorazepam)
    - Anticholinergics (e.g. benztropine, benzhexol)
    - Reduce antipsychotic dosage or switch to low potency agent
Typical / conventional antipsychotics

- **Adverse effects**
  - **Tardive dyskinesia (TD)**
    - Develops months to years after therapy
    - Involuntary choreoathetoid (twisting, writhing, worm-like) movements of tongue and face
    - Can interfere with chewing, swallowing and speaking
    - Symptoms are usually irreversible
Typical / conventional antipsychotics

- **Adverse effects**
  - Tardive dyskinesia (TD)

- **Management**
  - Some manufacturers suggest drug withdrawal at earliest signs of TD (fine vermicular movements of tongue) may halt its full development
  - Gradual drug withdrawal (to avoid dyskinesia)
  - Use lowest effective dose
  - Atypical antipsychotic for mild TD
  - Clozapine for severe, distressing TD
  - Inconsistent results with
    - Diazepam, clonazepam, valproate
    - Propranolol, clonidine
    - Vitamin E
Typical / conventional antipsychotics

- Other Adverse effects
  - Neuroleptic malignant syndrome (NMS)
    - Rare but serious reaction, 0.2% of patients on neuroleptics
    - High fever, autonomic instability, mental status changes, leaden rigidity, elevated CK, WBC, myoglobinuria
  - Management
    - Discontinue antipsychotic
    - Paracetamol for hyperthermia
    - IV fluids for hydration
    - Benzodiazepines for anxiety
    - Dantrolene for rigidity and hyperthermia
    - Bromocriptine for CNS toxicity
Typical / conventional antipsychotics

- Other Adverse effects
  - Neuroleptic malignant syndrome (NMS)
    - After symptom resolution
      - Some suggest to wait for at least 2 weeks before resuming
      - Use lowest effective dose
      - Avoid high potency agents
      - Consider atypical antipsychotics
    - However, NMS has been reported from patients taking clozapine, risperidone, olanzapine and quetiapine
Typical / conventional antipsychotics

- **Other Adverse effects**
  - **Prolactinemia**
    - D2 receptor blockade decreases dopamine inhibition of prolactin
    - Results in galactorrhea, amenorrhea, loss of libido
      - Managed with bromocriptine
  - **Sedation**
    - Administer once daily at bedtime
  - **Seizures**
    - Haloperidol has a lower risk of seizures
    - Anticonvulsants (beware or possible interaction with antipsychotic)
Atypical antipsychotics

- Refers to newer agents
- Also known as
  - Serotonin-dopamine antagonists
  - Postsynaptic effects at 5-HT2A and D2 receptors
Atypical antipsychotics

- Mechanism of action
  - Similar blocking effect on D2 receptors
  - Seem to be a little more selective, targeting the intended pathway to a larger degree than the others
  - Also block or partially block serotonin receptors (particularly 5HT2A, C and 5HT1A receptors)
  - Aripiprazole: dopamine partial agonist (novel mechanism)
Atypical antipsychotics

- Properties
  - Available evidence to show advantage for some (clozapine, risperidone, olanzapine) but not all atypicals when compared with typicals.
  - At least as effective as typicals for positive symptoms.
  - May be more efficacious for negative and cognitive symptoms (still under debate).
Atypical antipsychotics

- Properties
  - Less frequently associated with EPS
  - More risk of weight gain, new onset diabetes, hyperlipidemia
  - Novel agents, more expensive
Atypical antipsychotics

Potency

- All atypical antipsychotics are equally effective at therapeutic doses
  - Except clozapine
  - Most effective antipsychotic
  - For resistant schizophrenia
  - 2nd line due to life-threatening side effect
Atypical antipsychotics

Relative receptor-binding of atypical antipsychotics

<table>
<thead>
<tr>
<th>Drug</th>
<th>D1</th>
<th>D2</th>
<th>5-HT2</th>
<th>α1</th>
<th>M1</th>
<th>H1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clozapine</td>
<td>++</td>
<td>++</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
<td>+</td>
</tr>
<tr>
<td>Risperidone</td>
<td>-</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>++</td>
<td>++</td>
<td>+++</td>
<td>++</td>
<td>+++</td>
<td>++</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>-</td>
<td>+</td>
<td>++</td>
<td>+++</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Ziprasidone</td>
<td>+/-</td>
<td>++</td>
<td>+++</td>
<td>++</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Aripiprazole</td>
<td>+</td>
<td>+++</td>
<td>++</td>
<td>++</td>
<td>-</td>
<td>+</td>
</tr>
</tbody>
</table>
## Atypical antipsychotics

<table>
<thead>
<tr>
<th>Drug</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clozapine</td>
<td>For treatment-resistant cases, little EPS</td>
<td>Risk of fatal agranulocytosis</td>
</tr>
<tr>
<td>Risperidone</td>
<td>Broad efficacy, little or no EPS at low doses</td>
<td>EPS and hypotension at high doses</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>Effective with positive and negative symptoms, little or no EPS</td>
<td>Weight gain</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>Similar to risperidone, maybe less weight gain</td>
<td>Dose adjustment with associated hypotension, bd dosing</td>
</tr>
<tr>
<td>Ziprasidone</td>
<td>Perhaps less weight gain than clozapine, Inj A/V</td>
<td>QT prolongation</td>
</tr>
<tr>
<td>Aripiprazole</td>
<td>Less weight gain, novel mechanism potential</td>
<td>Uncertain</td>
</tr>
</tbody>
</table>
## Atypical antipsychotics

### Relative incidence of Adverse effects

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Sedation</th>
<th>EPS</th>
<th>Anticholinergic</th>
<th>Orthostasis</th>
<th>Seizure</th>
<th>Prolactin elevation</th>
<th>Weight gain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clozapine</td>
<td>++++</td>
<td>+</td>
<td>++++</td>
<td>+++</td>
<td>+++</td>
<td>0</td>
<td>+++</td>
</tr>
<tr>
<td>Risperidone</td>
<td>+++</td>
<td>+</td>
<td>++</td>
<td>+++</td>
<td>++</td>
<td>0 to +++</td>
<td>++</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>+++</td>
<td>+</td>
<td>+++</td>
<td>++</td>
<td>++</td>
<td>+</td>
<td>+++</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>+++</td>
<td>+</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>0</td>
<td>++</td>
</tr>
<tr>
<td>Ziprasidone</td>
<td>++</td>
<td>+</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>0</td>
<td>+</td>
</tr>
<tr>
<td>Aripiprazole</td>
<td>++</td>
<td>+</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>0</td>
<td>+</td>
</tr>
</tbody>
</table>
Atypical antipsychotics

- **1st line atypical antipsychotics**
  - All atypicals except clozapine
  - NICE recommendations
    - Atypical antipsychotics considered when choosing 1st line treatment of newly diagnosed schizophrenia
    - Treatment option of choice for managing acute schizophrenic episode
    - Considered when suffering unacceptable Adverse effects from a conventional antipsychotic
    - Changing to an atypical not necessary if typical controls symptoms adequately and no unacceptable Adverse effects
Atypical antipsychotics

- 2nd line atypical antipsychotic
  - Clozapine
    - Most effective antipsychotic for reducing symptoms and preventing relapse
    - Use of clozapine effectively reduce suicide risk
    - 1% risk of potentially fatal agranulocytosis
      - Acute pronounced leukopenia with great reduction in number of neutrophil
    - Clozapine should be introduced if schizophrenia is inadequately controlled despite sequential use of 2 or more antipsychotic (one of which should be an atypical) each for at least 6-8 weeks
Atypical antipsychotics

- Clozapine
  - Rare cases of myocarditis and cardiomyopathy
    - Fatal
    - Most commonly in first 2 months
  - CSM recommendations
    - Physical exam and medical history before starting
    - Persistent tachycardia esp. in first 2 weeks should prompt observation for cardiomyopathy
    - If myocarditis or cardiomyopathy, stop clozapine
    - Inform patients for unexplained fatigue, dyspnea, tachypnea, chest pain, palpitation and ask them to report these signs and symptoms immediately
Non-antipsychotic agents

- Benzodiazepines
  - Useful in some studies for anxiety, agitation, global impairment and psychosis
  - Schizophrenic patients are prone to BZD abuse
  - Limit use to short trials (2-4 weeks) for management of severe agitation and anxiety

- Lithium
  - Limited role in schizophrenia monotherapy
  - Improve psychosis, depression, excitement, and irritability when used with antipsychotic in some studies