The Basics of Clinical Psychopharmacology: Antipsychotic Medications

Dr. Roger Ho
The lecture is adopted from American Society of Clinical Psychopharmacology Model Curriculum for Medical Students
Authors

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Objectives

1. Discuss the common, currently available antipsychotics in Singapore with regard to clinical indications, presumed mechanism of action, common and serious adverse effects and cost.

2. Provide foundation to understand antipsychotics during clinical attachment.

3. Be able to name the basic drugs in the first generation and second generation antipsychotics.
Outline

1) Definition of the psychotic disorders
2) Review of the basic science of the drug class
3) Clinical case
4) The clinical psychopharmacology
5) Pitfalls and Pearls
6) Discussion Questions
Definition of psychotic disorders

A symptom of a major mental disorder in which:

- the personality is seriously disorganized
- contact with reality is usually impaired
- ability to think, perceive, and judge is impaired (often with delusions and/or hallucinations)
- ability to communicate and relate to others is impaired
- ability to cope with the environment is impaired
- ability to meet the ordinary demands of life is impaired
Types of Psychotic disorders

- Schizophrenia
- Bipolar Disorder with Psychotic Features
- Schizoaffective Disorder
- Major Depressive Disorder with Psychotic Features
- Psychosis due to Substance Abuse
- Psychosis due to a General Medical Condition
Diagnostic Criteria for Schizophrenia

- Characteristic Symptoms: 2 or more, each present for a significant proportion of the time for 1 month (or less if treated)
  - Delusions
  - Hallucinations
  - Disorganized Speech
  - Grossly disorganized or catatonic behavior
  - Negative symptoms (affective flattening, alogia, or avolition)
The Treatment of Psychosis

- Schizophrenia:
  - Antipsychotics

- Bipolar Disorder with Psychotic Features:
  - Mood stabilizers and/or antipsychotics

- Schizoaffective Disorder:
  - Antipsychotics, with mood stabilizers and/or antidepressants

- Major Depressive Disorder with Psychotic Features:
  - ECT and/or antidepressant medication and/or antipsychotic medication
The Treatment of Psychosis

- **Psychosis due to Substance Abuse intoxication/withdrawal:**
  Definitive treatment of substance abuse condition
  Antipsychotics as an adjunct for delirium

- **Psychosis due to a General Medical Condition (e.g., delirium):**
  Definitive treatment of general medical condition
  with antipsychotics as an adjunct
How do the antipsychotic drugs work?

All antipsychotics block the presynaptic D₂ autoreceptors, which increases neuronal electrical activity and release of dopamine.
The Dopamine Hypothesis

- Investigators noted that dopamine receptor antagonists inhibited amphetamine-induced activation and stereotypical behaviors of rodents. This effect has been found to be a reasonably reliable predictor of antipsychotic activity in humans.
The Dopamine Hypothesis—con’t

Moreover, agents associated with increased dopamine activity such as madopor or cocaine tend to cause psychosis or make it more severe.
Recent studies using highly selective D2-receptor ligands and PET indicate that dopamine receptor antagonists are effective when approximately 68% of D2 receptors in the brain are occupied.

Higher occupancy rates may be associated with more adverse effects without greater effectiveness.
The Dopamine Hypothesis—cont’d

- In contrast, clozapine (a second generation antipsychotic for treatment resistant schizophrenia) is effective when only 40 to 60% of D2 receptors are occupied.

- It has been suggested that activity at other receptors, particularly 5-HT2A receptors, may contribute to clozapine's clinical activity.
Two Types of Antipsychotics

- Typical Antipsychotics (1\textsuperscript{st} generation)
  also known as conventional antipsychotics
  e.g., chlorpromazine, haloperidol, trifluperazine

- Atypical Antipsychotics (2\textsuperscript{nd} generation)
  e.g., clozapine, risperidone, olanzapine, quetiapine ("atypical" because then are less likely to cause extrapyramidal side effects)
Typical Antipsychotics

- The modern era of psychopharmacology began with the discovery of chlorpromazine (Thorazine), the first effective antipsychotic, in the early 1950s.

- The dopamine receptor antagonists are antipsychotic rather than antischizophrenic. They are effective for treating psychosis, regardless of its cause.
Conventional/first generation/ “typical” antipsychotics (e.g., chlorpromazine, haloperidol, trifluoperazine)

- Dopamine (D2) receptor blockade
Typical Antipsychotics (1st generation): Definition

- Dopamine D2 blockers
- Produce extrapyramidal symptoms (EPS)
- Elevate prolactin (PRL) levels
- Equally effective but differ in potency/side effects (e.g. Haloperidol: more EPSE; chlorpromazine: more sedative)
- Largely effective for positive symptoms (e.g., delusions, hallucinations, disorganization of thought and behavior)
Common Typical Antipsychotics in Singapore

**Oral:**
- chlorpromazine (100-600mg/d)
- Trifluoperazine (5-10mg/d)
- haloperidol (5-20mg/d)

**Depot (monthly injection):**
Typical Antipsychotics

- These agents are highly effective for nearly all disorders that result in psychotic thought processes.
- However, they can cause acute and chronic neurological side effects that significantly limit their effectiveness.
- Evidence also suggests that treatment with antipsychotics can improve the long-term course of schizophrenia.
- They are relatively ineffective for the “negative symptoms” of schizophrenia.
Dopamine blockade and clinical effects of conventional agents

- 68% occupancy associated with efficacy
- 70% occupancy associated with hyperprolactinemia
- 80% occupancy associated with EPSE and akathisia
Mechanisms Of Side Effects

- EPSE & hyperprolactinemia—D$_2$ blockade
- Hypotension—alpha adrenergic blockade
- Sedation—histaminergic blockade
- Weight gain—histaminic & serotonergic blockade
- Anticholinergic (e.g., dry mouth)—muscarinic blockade
- Sexual side effects—serotonergic, muscarinic, noradrenergic and D$_2$ (via prolactin) blockade

Note: “Low-potency” agents have relatively higher affinities for these receptors (e.g., chlorpromazine)
Acute extrapyramidal symptoms (EPSE)

- Akathisia—a subjective feeling of restlessness
- Acute dystonic reactions—abrupt onset muscular spasms of the neck, eyes, trunk, extremities*
- Parkinsonism—stiffness, tremor, impaired gait

*Chronic dopamine blockade can lead to tardive dyskinesia (TD)
Tardive Dyskinesia (TD)

- A movement disorder that may occur following long-term treatment with antipsychotic medications.
- Movements may include:
  - mouth and tongue movements, such as lip smacking, sucking and puckering as well as facial grimacing
  - irregular movements of the limbs, particularly choreoathetoid-like movements of the fingers and toes and slow, writhing movements of the trunk
- TD is usually mild, but can be disabling, and is often irreversible.
Atypical Antipsychotics (2nd generation): Definition

- Share D2 and 5HT2A antagonism in common

- Addition of 5HT2A blockade may:
  - reduce EPSE
  - improve efficacy for negative symptoms
    e.g., withdrawal, flat affect, paucity of thought, avolition (poor initiation of goal directed behavior)
Risperidone: NUH provides 1mg and 2mg tablets: it is the first line treatment for psychosis.

2nd generation/“Atypical” antipsychotics (e.g., olanzepine, risperidone, quetiapine)

- Dopamine (D2) and Serotonin (5HT2A) blockade

Risperidone: NUH provides 1mg and 2mg tablets: it is the first line treatment for psychosis.
Atypical agents and D2 blockade

Atypical antipsychotics are effective with lower D$_2$ occupancy than traditional antipsychotics

- risperidone achieves 70% occupancy at approx 5 mg/day
- olanzapine achieves 70% occupancy at approx 20 mg/day
- clozapine and quetiapine do not exceed 60% occupancy
Indications

Atypical Antipsychotics

- Schizophrenia ("positive" & "negative" symptoms)
- Patient develops EPSE and TD
- Bipolar Disorder (with or without psychosis)
- Major Depression with Psychotic Features
- Agitation
- Delirium
## Atypical Antipsychotic Doses

<table>
<thead>
<tr>
<th>Drug</th>
<th>Typical Doses</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>risperidone (Risperdal)</td>
<td>0.5-6 mg qd</td>
<td></td>
</tr>
<tr>
<td>paliperidone (Invega)</td>
<td>3-12 mg per day</td>
<td></td>
</tr>
<tr>
<td>olanzapine (Zyprexa or Zydis)</td>
<td>15-30 mg per day</td>
<td></td>
</tr>
<tr>
<td>quetiapine (Seroquel)</td>
<td>300-800 mg per day</td>
<td></td>
</tr>
<tr>
<td>aripiprazole (Abilify)</td>
<td>15-30 mg per day ($15-30 /day)</td>
<td></td>
</tr>
<tr>
<td>clozapine (Clozaril)</td>
<td>300-900 mg / day</td>
<td>Prescriber/Patient must be registered; must check FBC regularly</td>
</tr>
</tbody>
</table>
Aripiprazole as partial agonist

![Image of Aripiprazole medication]

**Graph:**
- **Y-axis:** Maximum percentage response *in vitro*
- **X-axis:** Concentration (M)
- **Curves:**
  - 100 nM dopamine + aripiprazole
  - 100 nM dopamine + haloperidol
  - Aripiprazole

**Source:** Curr Med Res Opin © 2004 Librapharm Limited
The Uniqueness of Clozapine

- Effective in 30% of treatment-resistant patients at 6 weeks
- Minimal EPSE and risk of tardive dyskinesia
- Prevents relapse
- Stabilizes mood
- Improves polydipsia and hyponatremia
- Reduces hostility and aggression
- Reduces suicidality
- Possibly reduces cigarette smoking and substance abuse
- Because of agranulocytosis (rate 1/250) it is second line after two antipsychotics have failed.
Additional Receptor Activities of Atypical Antipsychotics (e.g., clozapine)

Clozapine also binds to:
- Other dopamine subtypes (D1, D3, D4)
- Alpha adrenergic (alpha 1&2)
- Histaminergic (H1)
- Muscarinic anticholinergic (M1)
- Other serotonergic subtypes (5HT1A, 2C, 6 & 7)
Agranulocytosis with clozapine

- US rate 0.38%
- Death rate 0.01%
- 80-85% of cases occur within the first 3 months
- 11-16% of cases occur between 3 and 6 months
- 4% of cases occur after the first 6 months
Effects on Prolactin Secretion

*Interference with dopamine secretion or action leads to an increase in serum prolactin*

<table>
<thead>
<tr>
<th>Medication</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Typicals</td>
<td>Increased</td>
</tr>
<tr>
<td>Risperidone</td>
<td>Increased</td>
</tr>
<tr>
<td>Clozapine</td>
<td>Little Increase</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>Little Increase</td>
</tr>
<tr>
<td>Ziprasidone</td>
<td>Little Increase</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>No Increase</td>
</tr>
<tr>
<td>Aripiprazole</td>
<td>No Increase (decrease?)</td>
</tr>
</tbody>
</table>
Clinical Consequences of Sustained Hyperprolactinemia

- Sexual dysfunction
- Amenorrhea
- Gynecomastia/Galactorrhea
- Hypoestrogenism/Osteopenia?
Estimated Weight Gain at 10 Weeks on “Standard” Dose

Weight Gain (lbs)

Clozapine
Olanzapine
Thioridazine
Chlorpromazine
Sertindole
Polypharmacy
Risperidone
Nonpharmacy
Haloperidol
Ziprasidone
Fluphenazine
Molindone
Placebo

D. B. Allison et al. *American J of Psych* 1999
Metabolic Syndrome

- Abdominal obesity
- Atherogenic dyslipidemia (blood fat disorders — high triglycerides, low HDL cholesterol and high LDL cholesterol)
- Elevated blood pressure
- Insulin resistance or glucose intolerance
- Prothrombotic state (e.g., high fibrinogen or plasminogen activator inhibitor–1)
- Proinflammatory state (e.g., elevated C-reactive protein)
## Incidence of Metabolic Syndrome on Atypical Antipsychotics

<table>
<thead>
<tr>
<th>Drug</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>olanzapine (Zyprexa)</td>
<td>high</td>
</tr>
<tr>
<td>quetiapine (Seroquel)</td>
<td>moderate</td>
</tr>
<tr>
<td>risperidone (Risperdal)</td>
<td>moderate</td>
</tr>
<tr>
<td>zisprazidone (Geodon)</td>
<td>low</td>
</tr>
<tr>
<td>aripiprazole (Abilify)</td>
<td>low</td>
</tr>
</tbody>
</table>
Long acting depot antipsychotics

- Can be administered in such a way that after a single dose a therapeutically efficient tissue concentration for 2 weeks to 1 month.

- Slow release of the active drug is produced by combining the base of antipsychotics with a fatty acid (decanoic acid).

- This is then used as a vehicle for the intramuscular injection where the ester which is not pharmacologically active is hydrolyzed by tissue esterases, slowly releasing the active compound.
Long acting depot antipsychotics—con’t

Depot preparations should be considered:

- For patients with several relapses who consistently default on oral medications
- In those patients who have clear cut compliance problems
- When oral absorption is poor due to idiosyncratic pharmacokinetic reactions
What Should We Monitor before and after I start a patient on antipsychotic?

- Physical Exam
  - Check weight - each visit
  - Check blood pressure - each visit
- ECG: baseline
- Lab Tests – baseline and every 6 months
  - Hemoglobin A1c
  - Fasting blood glucose
  - Triglycerides
  - Cholesterol
Mean change in QTc at steady state: (msec)
Abnormal value: Men>430ms; women > 450ms

<table>
<thead>
<tr>
<th>Drug</th>
<th>Change (msec)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ziprasidone</td>
<td>20.6</td>
</tr>
<tr>
<td>quetiapine</td>
<td>14.5</td>
</tr>
<tr>
<td>risperidone</td>
<td>10.0</td>
</tr>
<tr>
<td>olanzapine</td>
<td>6.4</td>
</tr>
<tr>
<td>Haloperidol</td>
<td>4.7</td>
</tr>
<tr>
<td>Aripiprazole</td>
<td>Minimal risk</td>
</tr>
</tbody>
</table>
Clinical Case Study

- A 24-year-old man is brought to the AED in 4 point restraints, after a 995 call by the patients’ parents who noted that he attempted to attack them while under the belief that they were involved in a government plot to kill him.

- The patient acknowledged the above, stating that he had received transmitted messages from aliens telling him to do this.

- The patient’s speech was so illogical that it was difficult to get further history directly from him.
Clinical Case Study—cont’d

- History obtained from family revealed that over the prior 6 months, the patient had slowly become more withdrawn and less involved in daily activities. The patient preferred solitude, becoming more detached from the family.

- Over the prior 6 months, the family reported that the patient slowly started exhibiting vague and circumstantial responses to questions. He was also preoccupied with receiving telepathic messages.

- Though suspicious and paranoid about other people, the patient did not exhibit aggressive behavior toward anyone.
Oral rapidly dissolvable tablets:

1. PO olanzapine 10mg stat

2. PO risperidone quicklet 2mg stat
What happens if oral dissolvable tablet does not work?

1. IM lorazepam 2mg stat

2. If IM lorazepam does not work, IM haloperidol 5mg stat.
Neuroleptic Malignant Syndrome (NMS)

- Idiosyncratic reaction to dopamine antagonists (more common in patients who are antipsychotic naïve)
- Capable of producing significant mortality
- Reported with essentially every D₁ or D₂ antagonist including non-psychotropics such as metoclopramide
NMS Diagnostic Criteria

Severe muscle rigidity and elevated temperature associated with the use of neuroleptic medication; and two (or more) of the following:

- diaphoresis
- dysphagia
- tremor
- Incontinence
- changes in level of consciousness ranging from confusion to coma
- mutism
- tachycardia
- elevated or labile blood pressure
- leukocytosis
- laboratory evidence of muscle injury (e.g., elevated CK)

abridged from DSM IV, p 742
NMS: A Diagnosis of Exclusion

- Must rule out catatonia and depression
- Must rule out general medical (e.g. infectious or neurologic) sources of fever and rigidity such as viral encephalitis
- Presence of viral encephalitis in some cases may have predisposed to development of NMS following brief neuroleptic exposure
Management of NMS

- Stop the antipsychotics.
- Supportive measures: IV hydration, cooling measures; transferal to ICU
- Bromocriptine: to reverse dopamine blockade.
- Dantrolene/lorazepam to reduce rigidity
- After stabilization, change to a different antipsychotics (less potent, e.g. quetiapine)
Reminders

- As a rule of thumb, start low and go slow
- Use very small doses for patients who are very sick
- Use very small doses for elderly patients
- For emergency use, know olanzapine zydis and haloperidol IM injection well. You will use it when you are a medical resident.
- Use combinations of these drugs with great caution
Question 1

What is the major neurotransmitter thought to be responsible for the efficacy of antipsychotic drugs?

A. serotonin
B. dopamine
C. norepinephrine
D. gamma-Aminobutyric acid
E. none of the above
Question 2

What makes the “atypical antipsychotics” atypical?

A. Different molecular structure
B. Different pharmacokinetics
C. Different metabolic pathway
D. Different side effect profile
E. Different dosage schedule
Question 3

What neurological symptom is not caused by the “typical” antipsychotics?

A. Tardive dyskinesia
B. Extra pyramidal symptoms
C. Acute dyskinesias
D. Pseudoparkinsonism
E. Expressive aphasia
Question 4

What would the best choice of antipsychotic be for a patient who has a lengthened QTc interval on ECG?

A. aripiprazole
B. risperidone
C. thioridazine
D. olanzapine
E. quetiapine
Question 5

Which statement about clozapine is true?

A. It is the original antipsychotic drug
B. It can lead to death from agranulocytosis in up to 0.1% of patients
C. There is little prolactin increase
D. There is little weight gain
E. It binds only to the D1, D3, and 5HT1A receptors
Answers to Questions

1. B
2. D
3. E
4. A
5. C
End of Lecture