The Future of Antipsychotic Therapy

(page 7 in syllabus)

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Speakers Bureau: Dainippon Sumitomo, Forest, Lilly, Merck, Pamlab, Pfizer, Sepracor/Sunovion, Servier, Wyeth
Learning Objectives

• Differentiate antipsychotic drugs from each other on the basis of their pharmacological mechanisms and their associated therapeutic and side effects

• Integrate novel treatment approaches into clinical practice according to best practices guidelines

• Identify novel therapeutic options currently being researched for the treatment of schizophrenia
Conventional (First-Generation) Antipsychotics

- D₂ antagonists
- Effective for positive symptoms
- Side effects
  - Extrapyramidal symptoms
  - Possible worsening of negative, cognitive, and affective symptoms

Chlorpromazine  Perphenazine
Cyamemazine   Pimozide
Flupenthixol   Pipothiazine
Fluphenazine   Sulpiride
Haloperidol    Thioridazine
Loxapine       Thiothixene
Mesoridazine   Trifluoperazine
Molindone      Zuclopenthixol

D₂ Receptor Occupancy Induced by Clinical Doses of Antipsychotic Drugs

<table>
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<th>Drug</th>
<th>Doses in mg/d</th>
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<th>No EPS</th>
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D₂ receptor occupancy (%)

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Hypothetical Thresholds for Antipsychotic Drug Effects

- EPS threshold
- Antipsychotic effect threshold

Dose; plasma concentration

D2 receptor blockade (%)
Antipsychotics at High Doses

• Although standard doses of all antipsychotics target 60-80% occupancy of D₂ receptors, this may not be sufficient to quell psychotic symptoms in all patients.

• Pharmacodynamic treatment failure for aggression associated with psychotic illness occurs when patients do not respond despite attaining 80% D₂ receptor occupancy with standard doses of antipsychotics.

• In these cases, clozapine or high doses of antipsychotics targeting more than 80% D₂ occupancy may be justified, especially if effective in reducing assaults and if side effects are carefully monitored.
Atypical (Second-Generation) Antipsychotics

• Potentially effective for treating positive, negative, affective, and cognitive symptom domains due to vast molecular polypharmacy

• Side effects
  – Cardiometabolic
  – Sedation
  – Various others


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Common Classes of Atypical Antipsychotics

SDA
- asenapine
- iloperidone
- olanzapine
- paliperidone
- perospirone
- risperidone
- sertindole
- zotepine

SPA
- clozapine
- quetiapine
- ziprasidone

DPA
- amisulpride?
- low-dose sulpiride?
- cariprazine
- aripiprazole
Molecular Basis of Side Effects

Functional Groups Responsible for Therapeutic Effects


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Molecular Basis of Side Effects

Functional Groups Responsible for Side Effects

Cardiometabolic side effects, including weight gain, insulin resistance, and increased fasting triglycerides.

EPS

Tardive Dyskinesia

Increased Prolactin


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The “-pines”: D2

![Graph showing receptor binding affinity of antipsychotic drugs with D2 receptors indicated.](image-url)
The “-pines”: 5HT2A
The “-pines”: 5HT1A, 2C, and 6
The “-pines”: 5HT7
The “-pines”: Alpha 1
The “-pines”: Alpha 2
The “-pines”: H1
The “-pines”: M1
The “-dones”: D2
The “-dones”: 5HT2A

Receptor Binding Affinity
Log of Ki values (nM)

- 5-HT2A
- D2
- risperidone
- paliperidone
- ziprasidone
- iloperidone
- lurasidone

Within 10 times Ki of D2

Low EPS
Low prolactin
The “-dones”: 5HT1A, 2C, and 6
The “-dones”: 5HT7
The “-dones”: Alpha 1

Receptor Binding Affinity
Log of Ki values (nM)

- 5-HT$_{2A}$
- α$_1$
- risperidone
- paliperidone
- ziprasidone
- iloperidone
- lurasidone

Within 10 times Ki of D$_2$
The “-dones”: Alpha 2
The “-dones”: H1
The “-dones”: M1

![Diagram showing receptor binding affinity with Ki values in nM](image)

- **Risperidone**
- **Paliperidone**
- **Ziprasidone**
- **Iloperidone**
- **Lurasidone**

Legend:
- **5-HT**
- **D2**
- **M1**

Note: The diagram illustrates the binding affinity within 10 times Ki of D2.
Aripiprazole: D2
Aripiprazole: 5HT2A
Aripiprazole: 5HT1A
Aripiprazole: 5HT7
Recently Approved Antipsychotic Treatments

ILOPERIDONE
ASENAPINE
LURASIDONE
Iloperidone

- Serotonin 5-HT$_{2A}$ / dopamine D$_2$ antagonist (SDA)
- Recently approved for acute treatment of schizophrenia in adults
Iloperidone

- Efficacy comparable to other AAPs
- Not approved for mania, but potentially effective
- Has very low placebo-level EPS and little or no akathisia
- Potent alpha 1 blocking properties suggest potential utility in PTSD
- Binding properties suggest theoretical efficacy in depression
- Long half-life suggests potential for once-daily dosing

- Limited registration data and real world clinical experience; follow slow titration
- Use caution with patients sensitive to orthostasis (young, elderly, patients with CV problems)
- In presence of potent 2D6 inhibitors (paroxetine, fluoxetine, duloxetine), reduce dose by half
- Weight gain/metabolic profile comparable to that of risperidone
- Dose-dependent QTc prolongation

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Asenapine

- Serotonin 5-HT$_{2A}$/dopamine D$_2$ antagonist (SDA)
- Currently approved for
  - Acute and maintenance treatment of schizophrenia in adults
  - Acute treatment of manic or mixed episodes associated with bipolar I disorder in adults
Asenapine

- Mild metabolic risk; no prolactin elevation
- No dose titration needed
- Long half-life; once-daily dose is theoretically possible
- Sublingual tablet good for reliable, compliant patient
- Not approved for depression, but binding profile suggests potential use in treatment-resistant cases

- Not absorbed once swallowed; must be administered sublingually
- Common side effect: oral hypoesthesia
- Patients may not eat or drink for 10 minutes after administration to increase bioavailability
- Somnolence/sedation, EPS
- Inhibits 2D6 and is a substrate for 1A2
Asenapine and Mirtazapine

- yellow = mirtazapine
- orange = asenapine

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Lurasidone

- Recently approved for schizophrenia in adults
- Lack of $H_1$ epitope suggests reduced risk of metabolic side effects and sedation
- $5$-HT$_7$ antagonism may be beneficial for cognitive and negative symptoms
Lurasidone

- Lack of affinity at H₁ and M₁ receptors allows treatment to begin at therapeutically effective dose; rapid onset of action
- EPS and akathisia, but seems to be reduced if taken at night
- 40-80 mg/day effective for acute exacerbation of schizophrenia
- Will require confirmation from real world clinical experience
- Appears to have benign metabolic profile without affecting QTc prolongation; low EPS
- Once-daily administration is possible

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Tandospirone and Lurasidone
5-HT\textsubscript{7} Receptor Distribution in Rat Brain

- Involved in numerous processes, including learning and memory
- Many atypical antipsychotics and antidepressants act at 5-HT\textsubscript{7} receptors
- Receptor levels are decreased in post-mortem schizophrenia cortex

5-HT$_7$ Receptors

- Depressive symptoms
- Circadian dysfunction
- Cognitive deficits
Possible Effects of 5-HT\textsubscript{7} Receptor Antagonism

- Reduced Depressive symptoms?
- Reduced Circadian dysfunction?
- Reduced Cognitive deficits?
5-HT$_7$
5-HT$_7$

![Diagram](attachment:image.png)
5-HT₇
Weight Change From Double-Blind Baseline
Median Change From Double-Blind Baseline in Metabolic Parameters
High-Dose Lurasidone: PANSS Total Score

Based on a repeated measures linear regression model of the change from Baseline score, with fixed effects for pooled center, visit as a categorical variable, baseline score, treatment and treatment by visit interaction, assuming an unstructured covariance matrix.
High-Dose Lurasidone: MADRS

<table>
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<tr>
<th>Group</th>
<th>Baseline</th>
<th>Mean change in MADRS</th>
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<tbody>
<tr>
<td>Placebo</td>
<td>11.8</td>
<td>-1.0</td>
</tr>
<tr>
<td>Lurasidone 80 mg/d</td>
<td>11.2</td>
<td>-4.0 ***</td>
</tr>
<tr>
<td>Lurasidone 160 mg/d</td>
<td>12.5</td>
<td>-4.4 ***</td>
</tr>
<tr>
<td>Quetiapine XR 600 mg/d</td>
<td>11.4</td>
<td>-4.3 ***</td>
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</table>

**p < 0.001**
High-Dose Lurasidone: Weight Increased by ≥ 7%
High-Dose Lurasidone: Cholesterol and Triglycerides

**Cholesterol**

- Placebo (n=111) -7.0
- Lurasidone 80 mg/d (n=111) -4.0
- Lurasidone 160 mg/d (n=114) -7.5
- Quetiapine XR 600 mg/d (n=107) +6.0

*** p<0.001

**Triglycerides**

- Placebo (n=111) -9.0
- Lurasidone 80 mg/d (n=111) -2.0
- Lurasidone 160 mg/d (n=114) -9.0
- Quetiapine XR 600 mg/d (n=106) +8.0

* p<0.05

Baseline: 132.3, 126.8, 127.5, 141.4
Emerging Antipsychotics and Novel Mechanisms of Action Under Investigation
## Investigational Mechanisms and Agents for Schizophrenia

<table>
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<th>Molecular Target</th>
<th>Clinical Target</th>
<th>Drug</th>
<th>Development Phase</th>
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<td>Dopamine 2/serotonin 2A</td>
<td>Positive, negative, and cognitive symptoms</td>
<td>sertindole</td>
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<td>Dopamine 3 antagonism</td>
<td>Positive, negative, and cognitive symptoms</td>
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<td>Glycine transport inhibition</td>
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<td>Positive and negative symptoms (adjunct)</td>
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<td>Positive allosteric modulation of glutamatergic AMPA receptors</td>
<td>Cognitive symptoms (adjunct)</td>
<td>farampator CX516</td>
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Cariprazine

- In Phase III clinical trials for schizophrenia and bipolar disorder
- Stronger affinity for D₃ over D₂ receptors
- Higher doses for schizophrenia and mania (antagonist actions)
- Lower doses for depression (agonist actions)
- Few metabolic side effects identified thus far
- Long-lasting metabolites have potential for long-acting formulations
Modulation of Glutamatergic Transmission

- Direct-acting glycine agonists
- mGluR 2/3 presynaptic agonist
- GlyT1 inhibitors (GRIs)

To be covered in glutamate lecture
Phosphodiesterase 10A

- Phosphodiesterases (PDEs) degrade cAMP and cGMP
  - Involved in many second messenger systems
- PDE10A is concentrated in striatum
- PDE 10A inhibitors lead to
  - Increased D₁ receptor functioning
  - Decreased D₂ receptor functioning
- Effective for positive, negative, and cognitive symptoms?

PDE 10A Inhibitors

Improvement in negative and cognitive symptoms?

Reduced positive symptoms?
Nicotinic Alpha 7 Agonists

- Reduced levels of alpha 7 receptors in schizophrenia
- Patients with schizophrenia often have diminished auditory sensory gating
  - May contribute to attentional impairment and perceptual disturbances
- Autosomal dominant polymorphism of the alpha 7 gene on 15q14 linked to cognitive impairments in schizophrenia
- Alpha 7 agonists increase cortical DA and may improve cognitive and negative symptoms
Nicotinic Alpha 7 Agonists

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Summary

- Conventional antipsychotics exert therapeutic and adverse actions via dopamine D₂ receptor antagonism.
- Atypical antipsychotics exert their therapeutic and adverse effects by binding to a variety of receptors, including dopamine D₂.
- Asenapine, iloperidone, and lurasidone are the most recently approved antipsychotics.
- Several novel mechanisms of action that go beyond D₂ receptor antagonism are under active investigation.