Switching antipsychotics:
Basing practice on pharmacology & pharmacokinetics

“L’imagination est plus important que le savoir”

Albert Einstein
Switching Antipsychotics: Objectives

Participants who complete this workshop will:

• Understand the implications for switching of antipsychotic receptor binding profiles & kinetics
• Be able to create safe & effective switching plans
• Be able to anticipate and prevent or manage adverse effects that may occur on switching

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Planning a switch

Objectives

- Minimise risk to patient’s mental stability
- Minimise potential adverse effects
- Anticipate potential problems and have management plan
- Ensure switch is completed
Case scenario: Phil*

- Diagnosis: bipolar-1 disorder
- Manic episode 3 months ago
- Currently being seen in clinic and by CPN
- Prescribed risperidone 6mg daily
- Problems with sexual function
- Wants to change to alternative that is less likely to impair sexual function

Work task

- Decide on an alternative antipsychotic to switch to
- What problems would you anticipate?
- Create a switching plan
- Give reasons for your decisions

* case for illustrative purposes only

Time available: 10 minutes
Key considerations when switching antipsychotics

- Pharmacodynamics
  - Predict adverse effects

- Pharmacokinetics
  - Predict withdrawal effects
  - Predict potential problems when switching
  - Switching plan
# Pharmacological Interventions in Psychosis

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Drug</th>
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</thead>
<tbody>
<tr>
<td>Dopamine D2 antagonism</td>
<td>1st generation antipsychotics</td>
</tr>
<tr>
<td>Dopamine D2 &amp; Serotonin 5-HT2a antagonism</td>
<td>Some 2nd generation antipsychotics</td>
</tr>
<tr>
<td>Antagonism at multiple receptors</td>
<td>Clozapine</td>
</tr>
<tr>
<td>Dopamine D2 &amp; D3 antagonism</td>
<td>Amisulpride</td>
</tr>
<tr>
<td>Dopamine D2 partial agonism</td>
<td>Aripiprazole</td>
</tr>
</tbody>
</table>
Key Dopamine Pathways

a. Mesolimbic pathway
b. Nigrostriatal pathway
c. Tuberinfundibular pathway
d. Mesocortical pathways

NA = Nucleus Accumbens

Based on:
Stahl SM, Mignon L
Antipsychotics: Treating Psychosis, Mania & Depression (2nd Edn)
Cambridge University Press 2010

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Hypotheses of Atypical Effects

- Ratio of $5HT_{2A} / D_2$ receptor binding
- Tight or loose binding at $D_2$ receptors
- Partial agonism at $D_2$ receptors
Hypotheses of Atypical Effects

1. **Ratio of 5HT$_{2A}$/D$_2$ receptor binding**
   - Atypical antipsychotics have a higher affinity for 5HT$_{2A}$ receptors than conventional antipsychotics

![Correlation Table]

Meltzer HY, Matsubara S, Lee JC.
The ratios of serotonin$_2$ and dopamine$_2$ affinities differentiate atypical and typical antipsychotic drugs.
Hypotheses of Atypical Effects

2. Tight or loose binding at D₂ receptors

<table>
<thead>
<tr>
<th>FAST OFF</th>
<th>MEDIUM</th>
<th>SLOW</th>
</tr>
</thead>
<tbody>
<tr>
<td>‘Atypical’ antipsychotics</td>
<td>First-generation antipsychotics</td>
<td></td>
</tr>
<tr>
<td>Amisulpride, Clozapine, Quetiapine</td>
<td>Olanzapine</td>
<td>Haloperidol, Chlorpromazine</td>
</tr>
</tbody>
</table>

Minutes for 50% release from cloned D₂ receptors

Seeman P
Atypical antipsychotics: mechanism of action
Hypotheses of Atypical Effects

3. Partial agonism at D2 receptors

Full agonist (dopamine)

Antagonist (haloperidol, olanzapine, etc)

Partial agonist (aripiprazole)

Partial receptor activity

Full receptor activity

Receptor activity blocked

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Tamminga CA
Partial dopamine agonists in the treatment of psychosis
J Neural Transm 2002;109:411-20
Approximate *absolute* receptor binding profiles of selected antipsychotics

**\( K_i \)** (nM) = nanomolar concentration of the antipsychotic required to block 50% of the receptors in vitro (i.e., lower number equals stronger receptor affinity/binding). Data based exclusively on human brain receptors. † Partial agonism

Based on: Correll CU. J Clin Psychiatry 2008;69 (suppl 4):26-36
Approximate *absolute* Dopamine $D_2$ binding of selected antipsychotics

$K_i$ (nM) = nanomolar concentration of the antipsychotic required to block 50% of the receptors in vitro (i.e., lower number equals stronger receptor affinity/binding). Data based exclusively on human brain receptors. † Partial agonism

Based on: Correll CU. J Clin Psychiatry 2008;69 (suppl 4):26-36

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Approximate *absolute* Dopamine D<sub>2</sub> & 5-HT<sub>2A</sub> binding of selected antipsychotics

$K_i$ (nM) = nanomolar concentration of the antipsychotic required to block 50% of the receptors in vitro (ie, lower number equals stronger receptor affinity/binding). Data based exclusively on human brain receptors. † Partial agonism

Based on: Correll CU. J Clin Psychiatry 2008;69 (suppl 4):26-36
Approximate *absolute* Dopamine D$_2$ & alpha-1 binding of selected antipsychotics

$K_i$ (nM) = nanomolar concentration of the antipsychotic required to block 50% of the receptors in vitro (i.e., lower number equals stronger receptor affinity/binding). Data based exclusively on human brain receptors. †Partial agonism

Based on: Correll CU. J Clin Psychiatry 2008;69 (suppl 4):26-36
Approximate *absolute* Dopamine D$_2$ & H$_1$ binding of selected antipsychotics

$K_i$ (nM) = nanomolar concentration of the antipsychotic required to block 50% of the receptors in vitro (ie, lower number equals stronger receptor affinity/binding). Data based exclusively on human brain receptors. † Partial agonism

Based on: Correll CU. J Clin Psychiatry 2008;69 (suppl 4):26-36

Are adverse effects likely within the dose spectrum required for antipsychotic effect?
Approximate absolute Dopamine D<sub>2</sub> & M<sub>1</sub> binding of selected antipsychotics

\[ K_i (\text{nM}) = \text{nanomolar concentration of the antipsychotic required to block 50% of the receptors in vitro} \]

Are adverse effects likely within the dose spectrum required for antipsychotic effect?

Based on: Correll CU. J Clin Psychiatry 2008;69 (suppl 4):26-36

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Predicting adverse effects from receptor binding profiles of antipsychotics

$K_i$ (nM) = nanomolar concentration of the antipsychotic required to block 50% of the receptors in vitro (i.e., lower number equals stronger receptor affinity/binding). Data based exclusively on human brain receptors. † Partial agonism

Based on: Correll CU. J Clin Psychiatry 2008;69 (suppl 4):26-36
Key considerations when switching antipsychotics

• Receptor binding
  – Predict adverse effects

• Pharmacokinetics
  – Predict withdrawal effects
  – Predict potential problems when switching
‘In general, it takes about 5 times the elimination half-life for a drug to reach steady state, and the same period for the drug to disappear from the plasma once it is discontinued at steady state.’

Correll CU, Eur Psychiatr 2010;25:S12-S21

Half-lives from Correll CU, Eur Psychiatr 2010;25:S12-S21
Approximate time to steady state

% of steady state concentration

1. $T\frac{1}{2}$ 12 hours

Time (hours)

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Approximate time to steady state

% of steady state concentration

1. $T\frac{1}{2}$ 12 hours
2. $T\frac{1}{2}$ 24 hours

Time (hours)
Approximate time to steady state

% of steady state concentration

1. T½ 12 hours
2. T½ 24 hours
3. T½ 72 hours

Time (hours)
Approximate elimination curves

Following abrupt discontinuation from steady state

% of drug remaining

1. T½ 12 hours
Approximate elimination curves

Following abrupt discontinuation from steady state

% of drug remaining

1. T½ 12 hours
2. T½ 24 hours
Approximate elimination curves

Following abrupt discontinuation from steady state

1. $T\frac{1}{2}$ 12 hours
2. $T\frac{1}{2}$ 24 hours
3. $T\frac{1}{2}$ 72 hours

% of drug remaining

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Effect of switching from longer to shorter half life drug

Drugs initiated or discontinued simultaneously

% of steady state concentration or drug remaining

2. T ½ 24 hours

T ½ 72 hours

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Effect of switching from shorter to longer half life drug

Drugs initiated or discontinued simultaneously

% of steady state concentration or drug remaining

T ½ 24 hours

T ½ 72 hours

Time (hours)

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Adverse effects observed when switching antipsychotics

Consider

• Receptor(s) that may be involved
  – Old drug
  – New drug

• Impact of drug half-lives
  – Old drug
  – New drug

• Effect associated with initiation of new drug?
  or

• Withdrawal effect of old drug?
Effects of receptor blockade

• Dopamine D2
  DESIRABLE
  Antipsychotic
  Anti-manic
  Anti-aggressive

• Muscarinic M1
  Anti-parkinsonism

• Alpha-1
  None

• Histamine H1
  Anxiolytic
  Sedation
  Sleep induction
  Anti-EPS / akathisia

UNDESIRABLE
Extrapyramidal side effects incl. tardive dyskinesia
Hyperprolactinaemia
Impaired memory / Cognition
Dry mouth
Orthostatic hypotension
Dizziness
Sedation

Adapted from: Correll CU
From receptor pharmacology to improved outcomes: individualising the selection, dosing, and switching of antipsychotics
European Psychiatry 2010;25:S12-S21
**Potential withdrawal effects**

- **Dopamine D2**
  - Rebound psychosis / mania
  - Agitation
  - Withdrawal akathisia
  - Withdrawal dyskinesia

- **Muscarinic M1**
  - Agitation / anxiety
  - Confusion
  - Insomnia
  - EPS / akathisia

- **Alpha-1**
  - Tachycardia
  - Hypertension

- **Histamine H1**
  - Anxiety
  - Agitation
  - Insomnia
  - Restlessness
  - EPS / akathisia

Adapted from: Correll CU
From receptor pharmacology to improved outcomes: individualising the selection, dosing, and switching of antipsychotics
European Psychiatry 2010;25:S12-S21
How should adverse effects on switching be managed?

- Rebound psychosis / mania
- Akathisia
- Dyskinesia
- Agitation / anxiety
- Insomnia

Consider
- Withdrawal effect?
- Effect of new drug?
- Short-term management
- Adjunctive treatments

Time available: 5 minutes
Management of adverse effects on switching

• **Rebound psychosis / mania**
  – Slow / reverse down-titration of prior antipsychotic
  – Add adjunctive treatment
  – Add benzodiazepine*

• **Agitation / anxiety**
  – Slow / reverse down-titration of prior antipsychotic
  – Add benzodiazepine* / antihistamine or antidepressant

• **Akathisia**
  – Slow / reverse down-titration of prior antipsychotic
  – Add benzodiazepine*

• **Insomnia**
  – Slow / reverse down-titration of prior antipsychotic
  – Restrict caffeine intake
  – Add benzodiazepine* / antihistamine

• **Dyskinesia**
  • Slow / reverse down-titration of prior antipsychotic

* short-term only

The use of an antihistamine may be helpful if the previous agent had significant antihistaminic activity.

Adapted from: Correll CU
From receptor pharmacology to improved outcomes: individualising the selection, dosing, and switching of antipsychotics
European Psychiatry 2010;25:S12-S21

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Planning a switch

Objectives

• Minimise risk to patient’s mental stability
• Minimise potential adverse effects
• Anticipate potential problems and have management plan
• Ensure switch is completed
# Drug half-lives & switching

<table>
<thead>
<tr>
<th>From</th>
<th>To</th>
<th>Potential problems</th>
<th>Switch strategy?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Short $T^{\frac{1}{2}}$</td>
<td>Short $T^{\frac{1}{2}}$</td>
<td>Withdrawal effects of first drug Side effects of new drug</td>
<td></td>
</tr>
<tr>
<td>Short $T^{\frac{1}{2}}$</td>
<td>Long $T^{\frac{1}{2}}$</td>
<td>Withdrawal effects of first drug Overlap period too short Side effects of new drug</td>
<td></td>
</tr>
<tr>
<td>Long $T^{\frac{1}{2}}$</td>
<td>Long $T^{\frac{1}{2}}$</td>
<td>Overlap period too short Low risk of withdrawal effects Side effects of new drug</td>
<td></td>
</tr>
<tr>
<td>Long $T^{\frac{1}{2}}$</td>
<td>Short $T^{\frac{1}{2}}$</td>
<td>Side effects from new drug Low risk of withdrawal effects</td>
<td></td>
</tr>
</tbody>
</table>
Case scenario: Phil, revisited

Work task

• Decide on an alternative antipsychotic to switch to
• What problems would you anticipate?
• Create a switching plan
• Give reasons for your decisions

Would you now approach this task differently?
What would you do that was different?
Conclusions

• Knowledge of both pharmacodynamics & pharmacokinetics is essential
  – To plan safe & effective switching
  – To help predict problems that may occur on switching
  – To help to determine the best management if problems are encountered
Thank you

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