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
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

Time available: 10 minutes

*case for illustrative purposes only
Key considerations when switching antipsychotics

- **Pharmacodynamics**
  - Predict adverse effects
  - Incident & Withdrawal 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>
</tr>
</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>
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 (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

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Key considerations when switching antipsychotics

• Receptor binding
  – Predict adverse effects
    • Incident & Withdrawal effects

• Pharmacokinetics
  – Predict withdrawal effects
  – Predict potential problems when switching
**Time to steady state or elimination (days)**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Half-lives</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risperidone</td>
<td>3 hours</td>
</tr>
<tr>
<td>Haloperidol</td>
<td>3-6 hours</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>6-7 hours</td>
</tr>
<tr>
<td>Clozapine</td>
<td>12 hours</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>30 hours</td>
</tr>
<tr>
<td>Aripiprazole</td>
<td>50-72 hours</td>
</tr>
</tbody>
</table>

‘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
Work task

• Draw graphs of approximate
  – Time to steady state following initiation
  – Elimination following discontinuation

• For 2 drugs:
  – Half-life of 20 hours
  – Half-life of 60 hours

Time available: 4 minutes
Approximate time to steady state

% of steady state concentration

1. T ½ 12 hours
2. T ½ 24 hours
3. T ½ 72 hours

Time (hours)

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Approximate elimination curves

Following abrupt discontinuation from steady state

% of drug remaining

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

Time (hours)
Questions:

• What are the potential problems of switching from a long half-life drug to a short half-life drug?

• What are the potential problems of switching from a short half-life drug to a long half-life drug?

• Consider:
  – Stability of patient’s mental state
  – Emergence of adverse effects

Time available: 5 minutes
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)
Adverse effects observed when switching antipsychotics

- Effect associated with initiation of new drug?
  or
- Withdrawal effect of old drug?

Consider
- Receptor(s) that may be involved
  - Old drug
  - New drug
- Impact of drug half-lives
  - Old drug
  - New drug
Effects of receptor blockade

- Dopamine D2
- Muscarinic M1
- Alpha-1
- Histamine H1

What are the likely withdrawal effects if antipsychotics are discontinued abruptly?

Consider
- Receptors involved
- Half-life

Time available: 5 minutes
Effects of receptor blockade

**Dopamine D2**
- Antipsychotic
- Anti-manic
- Anti-aggressive

**Muscarinic M1**
- Anti-parkinsonism

**Alpha-1**
- None

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

**Desirable**

**UNDESIRABLE**
- EPS
- Hyperprolactinaemia
- Impaired memory / cognition
- Dry mouth
- Postural hypotension
- Dizziness
- Sedation

**WITHDRAWAL**
- Rebound psychosis / mania
- Agitation
- Akathisia / Dyskinesia
- Agitation / anxiety
- Confusion
- EPS
- Insomnia
- Hypertension
- Tachycardia
- Anxiety
- Agitation / restlessness
- Insomnia
- 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

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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
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>
</table>
| Short $T\frac{1}{2}$ | Short $T\frac{1}{2}$ | Withdrawal effects of first drug  
Side effects of new drug | ?               |
| Short $T\frac{1}{2}$ | Long $T\frac{1}{2}$ | Withdrawal effects of first drug  
Overlap period too short  
Side effects of new drug | ?               |
| Long $T\frac{1}{2}$ | Long $T\frac{1}{2}$ | Overlap period too short  
Low risk of withdrawal effects  
Side effects of new drug | ?               |
| Long $T\frac{1}{2}$ | Short $T\frac{1}{2}$ | Side effects from new drug  
Low risk of withdrawal effects | ?               |

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# Pharmacokinetic data for selected LAIs

<table>
<thead>
<tr>
<th>FGAs</th>
<th>SGAs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluphenazine decanoate</td>
<td>Risperidone microspheres</td>
</tr>
<tr>
<td>Haloperidol decanoate</td>
<td>Paliperidone palmitate</td>
</tr>
<tr>
<td>Pipotiazine palmitate</td>
<td>Aripiprazole monohydrate</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Parameter</th>
<th>FGAs</th>
<th>SGAs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overlap with oral</td>
<td>1 week</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>4 weeks</td>
<td>3 weeks</td>
</tr>
<tr>
<td></td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>2 weeks</td>
<td>2 weeks</td>
</tr>
<tr>
<td>Time to peak plasma concentration</td>
<td>24 hours</td>
<td>4-5 weeks</td>
</tr>
<tr>
<td></td>
<td>3-9 days</td>
<td>12-16 days</td>
</tr>
<tr>
<td></td>
<td>9-10 days</td>
<td>5-7 days</td>
</tr>
<tr>
<td>Time to steady state</td>
<td>2-3 months</td>
<td>6-8 weeks</td>
</tr>
<tr>
<td></td>
<td>2-3 months</td>
<td>8-9 months</td>
</tr>
<tr>
<td></td>
<td>2-3 months</td>
<td>3-4 months</td>
</tr>
<tr>
<td>Apparent half-life</td>
<td>14 days</td>
<td>25-40 days (dose-related)</td>
</tr>
<tr>
<td></td>
<td>18-21 days</td>
<td>30 days (300mg dose)</td>
</tr>
<tr>
<td></td>
<td>14-21 days</td>
<td>46 days (400mg dose)</td>
</tr>
<tr>
<td>Usual dose interval</td>
<td>2 weeks</td>
<td>2 weeks</td>
</tr>
<tr>
<td></td>
<td>4 weeks</td>
<td>4 weeks</td>
</tr>
<tr>
<td></td>
<td>4 weeks</td>
<td>4 weeks</td>
</tr>
<tr>
<td></td>
<td>4 weeks</td>
<td>4 weeks</td>
</tr>
</tbody>
</table>

Data from various sources including CHMP assessment reports, SPCs and Psychotropic Drug Directory
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
Were the objectives met?

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