ADVANCED PSYCHOPHARMACOLOGY FOR FORENSIC ENVIRONMENTS
Learning Objectives: Treatment Resistant Psychosis

• Show how to use three critical endpoints in the management of treatment resistant psychosis: response, tolerability and futility

• Demonstrate how evidence-based uses of plasma antipsychotic levels define response and futility thresholds

• Discuss how the increased use of long acting injectables can enhance response in treatment resistant psychosis

• Propose ways to remove barriers to the use of clozapine
Recommended Practice

Inadequate response

High-dose antipsychotic monotherapy

Switch to different antipsychotic monotherapy*

Clozapine monotherapy

Antipsychotic polypharmacy

*Oral or long-acting injectable
Recommended Practice

Inadequate response

- Levels below therapeutic range
  - Adherent?
  - PK failure?
    - High-dose antipsychotic monotherapy

- Obtain plasma drug level of antipsychotic
  - Switch to different antipsychotic monotherapy*
    - Antipsychotic polypharmacy

- Clozapine monotherapy

PK = pharmacokinetic
*Oral or long-acting injectable
Recommended Practice

Inadequate response

Obtain plasma drug level of antipsychotic

Levels within therapeutic range
- No adverse effects
- PD failure?

High-dose antipsychotic monotherapy

Switch to different antipsychotic monotherapy*

Clozapine monotherapy

Antipsychotic polypharmacy

PD = pharmacodynamic
*Oral or long-acting injectable
1. Plasma levels and not dose are the best predictors of antipsychotic response
   • Clinical studies provide one source of plasma level/response relationships
   • For newer antipsychotics, PET scans provide data on plasma level thresholds to achieve 80% D₂ blockade

2. Antipsychotics typically have well-defined plasma level response thresholds below which likelihood of response is low
   • Upper limits are less well defined. What is reported by most labs is not evidence based.
CONCEPTS - What Labs Report As Upper Limits For Antipsychotic Levels Are Inconsistent And Inaccurate?

TABLE 4. Variations in laboratory plasma antipsychotic reference ranges

<table>
<thead>
<tr>
<th>Analyte</th>
<th>ARUP Lower</th>
<th>ARUP Upper</th>
<th>LabCorp Lower</th>
<th>LabCorp Upper</th>
<th>Mayo Clinic Lower</th>
<th>Mayo Clinic Upper</th>
<th>Quest Lower</th>
<th>Quest Upper</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluphenazine</td>
<td>0.5</td>
<td>2.0</td>
<td>1.0</td>
<td>10.0</td>
<td>1.0</td>
<td>10.0</td>
<td>Not provided</td>
<td></td>
</tr>
<tr>
<td>Haloperidol**</td>
<td>5.0</td>
<td>20.0</td>
<td>1.0</td>
<td>10.0</td>
<td>5.0</td>
<td>16.0</td>
<td>5.0</td>
<td>15.0</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>20.0</td>
<td>80.0</td>
<td>10.0</td>
<td>80.0</td>
<td>10.0</td>
<td>80.0</td>
<td>5.0</td>
<td>75.0</td>
</tr>
<tr>
<td>Clozapine ***</td>
<td>Not well established</td>
<td>Not provided</td>
<td>Therapeutic range &gt; 350 ng/ml</td>
<td>See below</td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

## RESPONSE AND FUTILITY THRESHOLDS

<table>
<thead>
<tr>
<th></th>
<th>Response Threshold (ng/ml)</th>
<th>Point of Futility (ng/ml)</th>
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</thead>
<tbody>
<tr>
<td>Haloperidol</td>
<td>3 - 5</td>
<td>30</td>
</tr>
<tr>
<td>Fluphenazine</td>
<td>0.8 – 1.0</td>
<td>4.0</td>
</tr>
<tr>
<td>Risperidone + 9-OH Risperidone</td>
<td>??</td>
<td>112</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>23.2</td>
<td>200</td>
</tr>
<tr>
<td>Clozapine</td>
<td>350</td>
<td>1000</td>
</tr>
</tbody>
</table>

CONCEPTS - 2

• Plasma levels should be obtained in the morning approximately 12 hrs after the bedtime dose.

• Even among adherent patients, levels may fluctuate up to 30%. Changes beyond this (when replicated) are usually due to nonadherence (or a new kinetic issue such as a med change).¹

• There are genetic variants of certain P450 enzymes (2D6, 1A2 especially) that are associated with ultrarapid metabolizer phenotypes.²

1. High plasma level antipsychotic Tx can be used for violent and treatment resistant schizophrenia pts who refuse or have failed a clozapine trial and who did not exhibit dose limiting side effects during routine antipsychotic exposure.

2. Antipsychotic treatment should be carefully titrated until one of 3 well-defined clinical endpoints are reached: clinical response, intolerability, or a point of futility.

   a. Treatment trials should not be routinely terminated on the basis of daily dose or high plasma levels: certain patients may both require and tolerate high doses and high plasma levels of D₂ antagonists.

   b. A small subset of schizophrenia patients have enormous tolerance for D₂ antagonism without EPS/akathisia. While not an absolute rule, consideration can be given for terminating a medication trial for futility with any of the following plasma levels:

      - haloperidol > 30 ng/mL
      - fluphenazine > 4.0 ng/mL
      - olanzapine > 200 ng/mL
Olanzapine
## Usual Doses to Achieve 60–80% D2 Occupancy

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OLANZAPINE: POINT OF FUTILITY ~ 200 NG/ML

RATIONALE:

1. In an 8-week fixed dose study of 50 mg/d olanzapine, the mean plasma level among the women was 278 ± 62 ng/ml. The primary adverse effect at higher plasma levels was constipation. ¹

2. A recent review of violent forensic inpatients noted few additional responders to plasma olanzapine levels > 200 ng/ml. ²

CASE: PSYCHOTIC VIOLENCE REQUIRING HIGH DOSE OLANZAPINE

• 44 yo AA female with schizophrenia charged with arson and battery on olanzapine 40 mg/d for several weeks with residual positive symptoms and aggression. Her plasma level is 78 ng/mL.
  • The lab reference range is 20-80 ng/mL. She is having some constipation.

Question: Should the patient’s dose be decreased, given more time to respond, increased, or add a second antipsychotic?
1. **Wait more time?**
   The patient continues to be highly symptomatic after 2 weeks on this dose. Therefore, more aggressive psychopharmacology is required.¹

2. **Decrease Dose?**
   Due to continued violence, do not decrease the dose. Treat the constipation aggressively.

3. **Increase Dose?**
   Increasing the dose (and level) is appropriate along with adequate treatment and monitoring of constipation. Levels up to 200 ng/ml (if tolerated) are recommended to treat psychosis.

4. **Add a second antipsychotic?**
   The best chance for response among failures of high plasma level olanzapine is clozapine. In a double-blind 8-week crossover study of olanzapine 50 mg/day vs. clozapine 450 mg/day, olanzapine response rates were 0%.²

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Risperidone and Paliperidone
• The active moiety (risperidone + 9-OH risperidone levels) is used. **The active moiety level is 7x the oral dose.**

• At steady state 81% of the active moiety is from 9-OH risperidone.

• The ratio of risperidone to 9-OH risp is usually 0.2 (range 0.1 – 0.3) in the CYP 2D6 extensive metabolizers.

## Usual Doses to Achieve 60–80% D2 Occupancy

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CASE: IS THIS AN ADEQUATE RISPERIDONE TRIAL?

• 62 yo WM with schizophrenia on risperidone 8 mg qhs for 2 months with ongoing positive Sx and no EPS. The is no lab reference range.

• Plasma levels:
  • Risperidone 9.3 ng/ml
  • 9-OH Risperidone 48 ng/ml
  • Active Moiety (Total) 57.3 ng/ml

Question 1: Are the levels expected based on the dose?

• The active moiety level should be 7x the oral dose or 56 ng/ml.

• In CYP 2D6 extensive metabolizers, the mean steady state ratio of risp:9-OH levels is 0.2 (range 0.1 – 0.3).² For this patient: 0.19

Although the patient is at > 80% D₂ occupancy, he has no EPS, and might benefit from a dose increase.

- The goal: make patient better or push drug levels to the point where side effects become limiting or a point of futility is reached (16 mg/d).

**Question:** Is it safe to give > 8 mg/d of risperidone? Isn’t the EPS threshold ~ 6 mg/d?

- **Answer:** It is safe. In the pivotal clinical trials doses up to 16 mg were used, and even on this high dose < 40% required benztropine.

D$_2$ Occupancy vs. Plasma 9-OH Risperidone Level

## Active Moiety Plasma Levels From Sustenna (9-OH Risperidone)

<table>
<thead>
<tr>
<th>Dose</th>
<th>Days (N)</th>
<th>Mean ± SD</th>
<th>Median</th>
<th>25&lt;sup&gt;th&lt;/sup&gt; Percentile</th>
<th>75&lt;sup&gt;th&lt;/sup&gt; Percentile</th>
</tr>
</thead>
<tbody>
<tr>
<td>39 mg</td>
<td>92 (n=78)</td>
<td>10.2 ± 8.5</td>
<td>8.9</td>
<td>5.7</td>
<td>11.1</td>
</tr>
<tr>
<td>156 mg</td>
<td>92 (n=84)</td>
<td>21.0 ± 13.0</td>
<td>18.6</td>
<td>10.8</td>
<td>25.5</td>
</tr>
<tr>
<td>234 mg</td>
<td>92 (n=88)</td>
<td>28.4 ± 14.9</td>
<td>27.0</td>
<td>16.1</td>
<td>35.1</td>
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Haloperidol Levels
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</tbody>
</table>

Global Improvement at the End of a Fixed Dose Haloperidol Study (n = 68)

<table>
<thead>
<tr>
<th>Plasma Level Range</th>
<th>Mean Plasma Level (ng/ml) ± SD</th>
<th>Very much improved or much improved on the CGI scale</th>
<th>% Improved</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 2 ng/ml</td>
<td>1.3 ± 0.5</td>
<td>1 out of 11</td>
<td>9%</td>
</tr>
<tr>
<td>2 - 5 ng/ml</td>
<td>3.2 ± 0.7</td>
<td>6 out of 14</td>
<td>43%</td>
</tr>
<tr>
<td>5 - 12 ng/ml</td>
<td>8.2 ± 1.6</td>
<td>22 out of 30</td>
<td>73%</td>
</tr>
<tr>
<td>&gt; 12 ng/ml</td>
<td>15.2 ± 2.7</td>
<td>5 out of 13</td>
<td>39%</td>
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</tbody>
</table>

RESPONSE TO HIGH PLASMA LEVELS: EXAMPLES

• Pt on haloperidol 45 mg/d has a plasma level 29.5 ng/mL AND no adverse effects. The lab has 20 ng/mL as the upper limit.
  
  • **Appropriate response**: recheck level, and if still high very slowly reduce the dose by no more than 10%/month. High levels of D₂ blockade may induce receptor supersensitivity; rapid dose reduction can result in rapid return of symptoms (known as supersensitivity psychosis).

  • **Inappropriate response**: reduce dose by 50% to get the level ≤ 20 ng/mL.
HALOPERIDOL EXAMPLE: REAL WORLD RESULT

Clinical data: this patient had no EPS or akathisia despite the level of 29.5 ng/ml, and was titrated to this haloperidol dose (and level) over several months.

The Outcome
• A new MD assumed care and decreased the haloperidol dose to 20 mg/d (plasma level 8.1 ng/ml). Over the next month, the patient deteriorated, started to refuse routine medication, and required numerous PRN medications for stability. The haloperidol dose was increased to 30 mg for several months, but the patient remained frequently assaultive.

The Lesson
• If the current level is tolerable, document this as the rationale for not drastically reducing the dose -> the patient may need this high level.
• If there is doubt whether the current plasma level was arrived at systematically, gradual dose reduction (e.g. 10%/month) is reasonable.
Haloperidol Decanoate: Conversion from Oral

- Studies using 10, 20, or 30 times the oral daily dose have been performed.
- 20 times the oral daily dose FOR MONTHLY MAINTENANCE provided optimum plasma concentrations DURING THE EARLY PHASE OF TREATMENT.
  - Oral haloperidol bioavailability is 65% (range 60-70%).
  - Example: pt on 10 mg/day x 30 days x 65% = 195 mg/month ~ 20 x oral daily dose.
- Over time, may be able to decrease the maintenance dose once steady state is reached based on plasma level monitoring.

100 mg Loading Study: 100 mg weekly x 4, 100 mg at weeks 6, 8, then 100 mg every 4 weeks starting wk 12

A pt with schizophrenia refuses oral medications and is violent. He is loaded with haloperidol decanoate 200 mg IM weekly over 3 weeks with excellent response and no adverse effects.

**Question 1:** What is the maintenance dose for this patient?

**Answer:** Based on the long-term data from the Jann 1996 study, the maintenance dose is 2x the weekly loading dose. For this pt, it will be 400 mg. Since injections of > 3 cc (300 mg) are not tolerated, the monthly dose will be given as 200 mg IM every 2 weeks.

**Question 2:** When is the maintenance dose started?

**Answer:** Based on the kinetic data from the Jann 1996 study, the maintenance dose should start 2 weeks after the last loading injection.
Clozapine
One of These Drugs Is Not Like the Others…

Multiple-Treatments Meta-Analysis

Making the Case for Using Clozapine Earlier: A Study in First-Episode Patients

Response: CGI of 1 or 2, and/or BPRS thought disorder subscale score ≤6

- TRIAL 1 n=244
  - olanzapine or risperidone
  - high proportion of response initially in first-episode patients

- TRIAL 2 n=60
  - olanzapine or risperidone
  - ≤20% response to second SGA in subgroup with poor response to first SGA

- TRIAL 3 n=28
  - clozapine
  - high proportion of response when switched to clozapine

CGI = Clinical Global Improvement. BPRS = Brief Psychiatric Rating Scale.
CLOZAPINE: DOPAMINE D₂ OCCUPANCY ISN’T AN IMPORTANT PART OF ITS EFFICACY

Uchida H, et al. Predicting dopamine D2 receptor occupancy from plasma levels of antipsychotic drugs. J Clin Psychopharmacol 2011; 31: 318-325
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37 yo Latino with schizophrenia on clozapine 500 mg/d for 8 weeks with ongoing positive symptoms. His plasma level is 773 ng/mL. The lab reference range is 200-700 ng/mL. There are no dose limiting adverse effects.

Question 1: Should the patient be given more time to respond, increase the dose or decrease the dose?
1. **Wait more time?**
   - In a standardized dose escalation protocol, every subject who responded met response criteria within an average 17 (± 14) days of a clozapine dose escalation (range 2 – 56 days).

2. **Increase Dose?**
   - With no viable alternatives to clozapine, and no dose limiting adverse effects, increasing the dose (and level) is appropriate.

3. **Decrease Dose?**
   - With no viable alternatives, the clozapine trial should be pursued until the patient responds or dose limiting adverse effects occur. Seizures, constipation (even with ileus) and diabetes mellitus are not reasons to stop clozapine.

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There is an upper threshold beyond which the likelihood of response is poor versus the likelihood of leading to side effects. For clozapine the limiting side effects are not EPS, but sedation, orthostasis.

- **Remington (2013):** 838 ng/ml \(^1\) Source: community sample
- **Meyer (2014):** 1000 ng/ml \(^2\) Source: violent forensic inpatients

RESPONSE TO HIGH PLASMA LEVELS: EXAMPLES

- Pt on clozapine 400 mg/d has a plasma level 1500 ng/mL. He denies sialorrhea, constipation or other adverse effects. The lab has 700 ng/mL as the upper limit.
  - **Appropriate response:** recheck level, and if still high very slowly reduce the dose. Clozapine does not induce D₂ receptor supersensitivity, but rapid dose reduction may cause cholinergic rebound.
  - **Inappropriate response:** reduce dose by 50% to get the level ≤ 700 ng/mL.
Clozapine Is Underused: Why?

- Clozapine use in the US\(^1\)
  - 5.5% of treatment-resistant patients

- Mean delay from meeting NICE criteria for treatment-resistant to clozapine initiation: 4 years\(^2\)

- Before commencing clozapine:\(^2\)
  - Antipsychotic polypharmacy: 36%
  - High-dose treatment: 34%

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Tricks of the Trade for Clozapine:
(The secret is knowing how to manage side effects)

Getting Started

• Constipation
  • Aggressive proactive treatment

• Sialorrhea
  • Botox clinic

• Neutropenia
  • Understand benign ethnic neutropenia
  • Monitor and respond

Becoming an Expert

• Learn how to manage the other side effects
• Consult the literature/handbooks

RESPONSE TO HIGH PLASMA LEVELS

A. How does the patient look? Does their appearance correlate with the plasma level? Are there any new or worse adverse effects?

B. Does the level make sense?

1) Is this level consistent with other levels?

Example: pt on clozapine 550 mg/d has level of 1200 ng/ml. Prior level on 500 mg/d was 750 ng/ml. No other med changes, and no new or worse adverse effects.

2) Has there been a dose increase, addition of an inhibitor or removal of an inducer?

Example: patient on haloperidol + phenytoin since 1978 gets new neurologist who changes phenytoin to levetiracetam

RESPONSE TO HIGH PLASMA LEVELS

1. **No dose change:** if no adverse effects and the level appears inconsistent with other levels (i.e. suspect lab error), **document** this as the rationale for maintaining the status quo and rechecking the level.

2. **No dose change:** if no adverse effects and the level appears consistent with other levels **document** this as the rationale for maintaining status quo *for now*, rechecking the level and planned slow dose decrease.

3. **Reduce dose:** if adverse effects, reduce dose to the prior tolerated dose (and level) and recheck level at steady state on that dose.
Summary

1. Clinical antipsychotic response correlates better with plasma antipsychotic levels than with oral dose
2. Knowing minimum and futility levels of key antipsychotics can guide dosing in treatment resistant patients
3. Long acting injectables can not only assure plasma drug levels, but understanding how to use first generation agents can allow attaining levels of D2 receptor occupancy not easily attained with second generation injectables
4. Knowing not only how to dose but also how to manage side effects is the trick for getting more out of clozapine for treatment resistant patients
What is/are the tricks of the trade for managing psychosis resistant to treatment with several antipsychotics?

1. Clozapine
2. High Dosing
3. Plasma drug levels
4. None of the above
What correlates best with antipsychotic efficacy?

1. Oral dosing
2. Injectable dosing
3. Plasma drug levels
4. All of the above
5. None of the above
Posttest Question

In the California Dept of State Hospitals with almost all patients having a psychotic illness, what is the most common cause of treatment resistance?

1. Inadequate dosing within approved dose range
2. Pharmacokinetic failure
3. Pharmacodynamic failure
4. Intolerability
5. Lack of adherence