Modern Use of Plasma Antipsychotic Levels

Faculty

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Disclosures

Jonathan Meyer, MD (Chair)
Dr. Meyer reports having received speaking or advising fees from Acadia Pharmaceuticals, Alkermes, Allergan, Forum Pharmaceuticals, Merck, Neurocrine, Otsuka America, Inc., Sunovion Pharmaceuticals and Teva Pharmaceutical Industries.

Jennifer O'Day, MD
None

Eric Schwartz, MD
None

Agenda

1. Limitations and Principles of Plasma Antipsychotic Data; Use of Levels to Monitor Adherence - Jonathan Meyer MD
2. Interpretation of Plasma Haloperidol and Fluphenazine Levels - Eric Schwartz MD
3. Interpretation of Plasma Risperidone and 9-OH Risperidone Levels - Jonathan Meyer MD
4. Interpretation of Plasma Olanzapine and Clozapine Levels - Jennifer O'Day MD
5. Concluding Remarks - Jonathan Meyer MD
6. Question and Answer - Panel
Learning Objectives

1. At the conclusion of this session, the participant will be able to: understand the limitations of cross-sectional plasma antipsychotic data to guide treatment decisions

2. At the conclusion of this session, the participant will be able to: understand the relationship between D2 occupancy and antipsychotic plasma levels

3. At the conclusion of this session, the participant will be able to: understand how to combine information from antipsychotic plasma levels with the clinical picture to determine an appropriate course of action

Basic Concepts
Concepts

- 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% \( D_2 \) blockade
Clinical Unknowns That Impact Relationships Between Antipsychotic Response and Dose

- P450 genetics of patients are usually unknown
- Some patients are nonadherent
- Many patients receive concurrent medications that are P450 or PGP inhibitors or inducers
  - The extent of these effects may be estimated from the literature, but may be complex when several agents are involved

- **NET RESULT** -> Dose is often a poor predictor of plasma level.

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Example: Lurasidone

Factors Influencing Plasma Levels

- **Medications that inhibit or induce P450 3A4**
  - Strong inhibitors: increase AUC 9-fold
  - Moderate Inhibitors: increase AUC 2-fold
  - Strong Inducers: decrease AUC 80%

- **Food**
  - 350 Kcal meal: increases AUC 2-fold

Potkin SG, et al. CNS Spectrums 2013
Lurasidone D$_2$ Occupancy

Conclusion from PET Study:

D$_2$ occupancy correlates poorly with dose, but very well with plasma level of the active moiety.

Potkin SG, et al. CNS Spectrums 2013

D$_2$ Occupancy Sweet Spot: 60%-80%

Thresholds for Response, Tolerability and Futility

<table>
<thead>
<tr>
<th>Drug</th>
<th>Response Threshold (ng/ml)</th>
<th>Tolerability Threshold (ng/ml)</th>
<th>Level associated with 60% D₂ occupancy</th>
<th>Level associated with 80% D₂ occupancy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haloperidol</td>
<td>3 - 5</td>
<td>18 – 20</td>
<td>1.2</td>
<td>2.0</td>
</tr>
<tr>
<td>Fluphenazine</td>
<td>0.8 – 1.0</td>
<td>2.7 – 2.8</td>
<td>??</td>
<td>??</td>
</tr>
<tr>
<td>Risperidone + 9-OH Risperidone</td>
<td>??</td>
<td>??</td>
<td>~ 17 ng/ml</td>
<td>45-47</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>23.2</td>
<td>176</td>
<td>~ 20 ng/ml</td>
<td>70-78</td>
</tr>
<tr>
<td>Clozapine</td>
<td>350</td>
<td>? 800-1000</td>
<td>??</td>
<td>??</td>
</tr>
</tbody>
</table>

Does Everyone Eventually Get EPS?

• The clinical rule for decades was to titrate to EPS and then reduce the dose.
• To examine the degree of variability in the EPS threshold, a controlled trifluoperazine titration study was performed in 1968.
• 10 male patients with schizophrenia were started on trifluoperazine 15 mg/d (equivalent to 6 mg haloperidol) without antiparkinsonian treatment, and advanced by 10 mg per week until they reached a predefined level of neurological adverse effects.


Not Everyone Gets EPS: Subject 5

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (Years)</th>
<th>Length of Hospitalization (Years)</th>
<th>Maximum Daily Trifluoperazine Dose (mg)</th>
<th>Degree of Psychiatric Improvement</th>
<th>Maximum Neurological Rating</th>
<th>Weight Change (lbs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>35</td>
<td>16</td>
<td>30</td>
<td>-</td>
<td>3.0</td>
<td>-5</td>
</tr>
<tr>
<td>2</td>
<td>52</td>
<td>31</td>
<td>150</td>
<td>-</td>
<td>1.2</td>
<td>5</td>
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<tr>
<td>3</td>
<td>52</td>
<td>27</td>
<td>100</td>
<td>0</td>
<td>1.5</td>
<td>-3</td>
</tr>
<tr>
<td>4</td>
<td>23</td>
<td>6</td>
<td>220</td>
<td>+</td>
<td>1.1</td>
<td>25</td>
</tr>
<tr>
<td>5</td>
<td>30</td>
<td>11</td>
<td>480</td>
<td>+</td>
<td>0.4</td>
<td>30</td>
</tr>
<tr>
<td>6</td>
<td>41</td>
<td>23</td>
<td>100</td>
<td>±</td>
<td>1.1</td>
<td>10</td>
</tr>
<tr>
<td>7</td>
<td>51</td>
<td>14</td>
<td>20</td>
<td>+</td>
<td>3.1</td>
<td>10</td>
</tr>
<tr>
<td>8</td>
<td>57</td>
<td>16</td>
<td>30</td>
<td>+++</td>
<td>2.0</td>
<td>12</td>
</tr>
<tr>
<td>9</td>
<td>42</td>
<td>11</td>
<td>40</td>
<td>±</td>
<td>2.0</td>
<td>12</td>
</tr>
<tr>
<td>10</td>
<td>55</td>
<td>32</td>
<td>60</td>
<td>+</td>
<td>2.0</td>
<td>6</td>
</tr>
<tr>
<td>Mean</td>
<td>43.8</td>
<td>18.7</td>
<td>123</td>
<td>1.74</td>
<td>10.2</td>
<td></td>
</tr>
</tbody>
</table>

The Point of Futility

• **Conclusion:** For a small subset of patients the EPS threshold may never be reached.

• Based on this observation, there is probably a point of futility for most antipsychotics beyond which the likelihood of response is virtually nil:
  • Haloperidol > 30 ng/mL
  • Fluphenazine > 4.0 ng/mL
  • Olanzapine > 200 ng/mL


Is My Patient Adherent With Oral Medication
Levels and Adherence

- Clinicians grossly underestimate medication adherence. Using 70% as the threshold for medication adherence, 57% of chronic schizophrenia patients are nonadherent using MEMS cap technology, patient self-report is 5%, and physician estimate 7%.1

- Many patients characterized as treatment resistant have subtherapeutic plasma levels.2

“The purpose of the present study was to determine the extent of subtherapeutic antipsychotic plasma levels in a group of patients clinically identified as treatment-resistant. Antipsychotic plasma levels were measured in 36 patients identified as having treatment-resistant schizophrenia by their treating clinicians. Sixteen (44%) patients showed either undetectable (19%) or subtherapeutic levels (25%), and 20 (56%) patients had levels in the therapeutic range.”


Oral Dose-Plasma Level Relationships

Concentration (ng/ml) = 12 x oral dose (mg/d)

Aripiprazole/Dehydroaripiprazole Ratio: 4.4 (range 3.6 - 5.0)

<table>
<thead>
<tr>
<th>Aripiprazole</th>
<th>Dehydroaripiprazole</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 mg/d -&gt;</td>
<td>126 ± 78 ng/ml</td>
</tr>
<tr>
<td>20 mg/d -&gt;</td>
<td>230 ± 193 ng/ml</td>
</tr>
<tr>
<td>30 mg/d -&gt;</td>
<td>400 ± 236 ng/ml</td>
</tr>
</tbody>
</table>

- 40 year old male, 80 kg, clozapine/norclozapine ratio of 1.32

Concentration (ng/ml) = 1.08 x oral dose (mg/d) (nonsmokers)

<table>
<thead>
<tr>
<th>Concentration (ng/ml) = 0.67 x oral dose (mg/d) (smokers)</th>
</tr>
</thead>
<tbody>
<tr>
<td>325 mg -&gt; 350 ng/ml (nonsmokers)</td>
</tr>
<tr>
<td>525 mg -&gt; 350 ng/ml (smokers)</td>
</tr>
</tbody>
</table>

Clozapine

- 40 year old female, 70 kg, clozapine/norclozapine ratio of 1.32

Concentration (ng/ml) = 1.32 x oral dose (mg/d) (nonsmokers)

<table>
<thead>
<tr>
<th>Concentration (ng/ml) = 0.80 x oral dose (mg/d) (smokers)</th>
</tr>
</thead>
<tbody>
<tr>
<td>265 mg -&gt; 350 ng/ml (nonsmokers)</td>
</tr>
<tr>
<td>435 mg -&gt; 350 ng/ml (smokers)</td>
</tr>
</tbody>
</table>

Haloperidol

<table>
<thead>
<tr>
<th>Concentration (ng/ml) = 0.78 x oral dose (mg/d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 mg/d -&gt; 1.57 ± 1.42 ng/ml</td>
</tr>
<tr>
<td>10 mg/d -&gt; 7.79 ± 4.79 ng/ml</td>
</tr>
</tbody>
</table>

Oral Dose-Plasma Level Relationships

<table>
<thead>
<tr>
<th>Drug</th>
<th>Concentration (ng/ml) = k x oral dose (mg/d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluphenazine</td>
<td>0.08 x oral dose (mg/d) (nonsmokers)</td>
</tr>
<tr>
<td></td>
<td>0.04 x oral dose (mg/d) (smokers)</td>
</tr>
<tr>
<td>Concentration (ng/ml) = 2.00 x oral dose (mg/d) (nonsmokers)</td>
<td></td>
</tr>
<tr>
<td>Concentration (ng/ml) = 1.43 x oral dose (mg/d) (smokers)</td>
<td></td>
</tr>
<tr>
<td>Olanzapine</td>
<td>7.00 x oral dose (mg/d)</td>
</tr>
<tr>
<td>Risperidone + 9-OH Risperidone (active moiety)</td>
<td>C/D Ratio = 7.05</td>
</tr>
<tr>
<td></td>
<td>6 mg/d -&gt; C/D Ratio = 7.15</td>
</tr>
<tr>
<td></td>
<td>10 mg/d -&gt; C/D Ratio = 7.28</td>
</tr>
<tr>
<td></td>
<td>16 mg/d -&gt; C/D Ratio = 6.95</td>
</tr>
</tbody>
</table>


Comments

• 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 kinetic issues. ¹

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

• Less than 50% of outpatients with schizophrenia are 80% adherent with oral medication. ³

Case: Is My Patient Taking His Olanzapine?

- 34 year old Latino nonsmoking male with schizophrenia discharged from hospital on olanzapine 20 mg qhs. No plasma levels were obtained in the hospital.
- He is new to my clinic and appears stable for the first month. On today’s morning visit he is more symptomatic, and denies missing doses, using substances, smoking or new stressors.
- A plasma level is instantly obtained (!!) and is reported as 15 ng/ml.

Question: What level is expected based on the dose?


Risperidone and Paliperidone
Risperidone – Basics

- Active moiety level (ng/ml) = 7.0 x oral dose (mg)
- Risp/9-OH Risperidone Ratio = 0.2 (range 0.1 - 0.3)
- Level Associated with 50% D₂ Antagonism: 17 ng/ml
- Level Associated with 80% D₂ Antagonism: 45-47 ng/ml
- Point of futility: probably > 112 ng/ml (16 mg/d oral)

Risp + 9-OH Risp Levels in Consta Studies (ng/ml)

<table>
<thead>
<tr>
<th>Consta Dose</th>
<th>12 Wk Study¹</th>
<th>52 Wk Study²</th>
<th>26 Wk Study³</th>
<th>Oral Risp Equivalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>25 mg</td>
<td>18.7 ± 9.23</td>
<td>18.1 ± 16.1</td>
<td>--</td>
<td>2.63 mg</td>
</tr>
<tr>
<td>50 mg</td>
<td>35.5 ± 18.7</td>
<td>32.2 ± 18.0</td>
<td>29.6 ± 15.8</td>
<td>4.63 mg</td>
</tr>
<tr>
<td>75 mg</td>
<td>44.7 ± 20.6</td>
<td>47.4 ± 27.6</td>
<td>--</td>
<td>6.58 mg</td>
</tr>
<tr>
<td>100 mg</td>
<td>--</td>
<td>--</td>
<td>62.4 ± 38.0</td>
<td>8.91 mg</td>
</tr>
</tbody>
</table>

9-OH Risp Level in a 13-wk Sustenna Study (day 92) ⁴

<table>
<thead>
<tr>
<th>Sustenna Dose</th>
<th>Mean ± SD</th>
<th>Median</th>
<th>25th % ile</th>
<th>75th % ile</th>
<th>Mean Oral Risp Equivalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>39 mg (n=78)</td>
<td>10.2 ± 8.5</td>
<td>8.9</td>
<td>5.7</td>
<td>11.1</td>
<td>1.5 mg</td>
</tr>
<tr>
<td>156 mg (n=84)</td>
<td>21.0 ± 13.0</td>
<td>18.6</td>
<td>10.8</td>
<td>25.5</td>
<td>3.0 mg</td>
</tr>
<tr>
<td>234 mg (n=88)</td>
<td>28.4 ± 14.9</td>
<td>27.0</td>
<td>16.1</td>
<td>35.1</td>
<td>4.0 mg</td>
</tr>
</tbody>
</table>

Case: Is This an Adequate Trial of Risperidone?

- 62 yo white male with schizophrenia on Consta 75 mg IM q 2 wks > 4 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?**

- Yes, in a 12-month trial, the mean active moiety level on 75 mg IM q 2 weeks was 47.4 ± (27.6) ng/ml. ¹
- 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**

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**Question: What is the D₂ Occupancy for this Risperidone Plasma Level?**

[Graph showing D₂ Receptor Occupancy (%) vs. Risperidone + 9-Hydroxyrisperidone Level (ng/ml)]


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Case: What to Do?

• **Option 1:** Although the patient is at > 80% D2 occupancy, he has no EPS, and might benefit from a further dose increase.
  - The goal: make patient better or push drug levels to the point where side effects become limiting.
  - **Question:** is it safe to give 100 mg Consta IM q 2 weeks?
    • **Answer:** yes, and the levels are comparable to 6-8 mg/d oral risperidone

  **Active moiety levels from a 6-month trial** *
  - 50 mg: 29.63 ± 15.81
  - 100 mg: 62.36 ± 38.01

  **Problem:** 75 mg Consta q 2 wks = $50,000/yr
  • To obtain more D2 blockade need to supplement with oral risperidone, or try typical depot

Meltzer HY, et al. A six month randomized controlled trial of long acting injectable risperidone 50 and 100 mg in treatment resistant schizophrenia. Schiz Res 2014; 154: 14-22

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Case: What to Do?

• **Option 2:** Go to a more effective medication
  - **Issues:** for those who are considered risperidone nonresponders, olanzapine will pick up another 7-9% more responders, and clozapine up to 60%

  **Problem:** Relprevv (olanzapine pamoate) is not widely available and there is no clozapine depot.

**Positive thoughts** *(or wishful thinking):* since this patient has not reached his EPS/tolerability threshold, perhaps he may respond with supplemental oral risperidone, or a typical depot
Interpretation of Plasma Haloperidol and Fluphenazine Levels

Oral Antipsychotic Concentration/Oral Dose Relationships

<table>
<thead>
<tr>
<th>Drug</th>
<th>Relationships and Supporting Data</th>
</tr>
</thead>
</table>
| Haloperidol | Concentration (ng/ml) = 0.78 x oral dose (mg/d)  
2 mg/d -> 1.57 ± 1.42 ng/ml  
10 mg/d -> 7.79 ± 4.79 ng/ml  |
| Fluphenazine | Concentration (ng/ml) = 0.08 x oral dose (mg/d) (nonsmokers)  
Concentration (ng/ml) = 0.04 x oral dose (mg/d) (smokers)  
22.9 mg -> 1.83 ± 0.94 ng/ml  
20.4 mg -> 0.89 ± 0.43 ng/ml  |

Probability Curves of Response and Disabling Side Effects by Plasma Fluphenazine Level

Fluphenazine Levels and $D_2$ Occupancy

<table>
<thead>
<tr>
<th>Plasma Fluphenazine Level</th>
<th>Striatal Occupancy</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.23 ng/mL(^1)</td>
<td>89%</td>
</tr>
<tr>
<td>4.4 ng/mL(^2)</td>
<td>92% R, 100% L</td>
</tr>
<tr>
<td>5.2 ng/mL(^2)</td>
<td>100% R, 97% L</td>
</tr>
<tr>
<td>6.13 ng/mL(^1)</td>
<td>91%</td>
</tr>
<tr>
<td>7.88 ng/mL(^1)</td>
<td>92%</td>
</tr>
<tr>
<td>11.38 ng/mL(^1)</td>
<td>96%</td>
</tr>
<tr>
<td>16.19 ng/mL(^1)</td>
<td>97%</td>
</tr>
</tbody>
</table>

1. Nyberg S et al. D(2) and 5-HT(2) receptor occupancy in high-dose neuroleptic-treated patients IJNP 1998;1:95-101
2. Coppens HJ et al. High central D2-dopamine receptor occupancy as assessed with positron emission tomography in medicated but therapy-resistant schizophrenic patients Biol Psychiatry 1991;29:629-34
Haloperidol: Response and Plasma Levels in Clinical Studies

- Trials in the 1970s and early 1980s showed response threshold 3-5 ng/ml with upper limit of 15-20 ng/ml

Haloperidol: Probability of Adverse Effects in Clinical Studies

Case: The Haloperidol Level of 29.5 ng/mL

- 50 yo AA female with schizophrenia on haloperidol oral 45 mg/d with plasma level 29.5 ng/mL. The lab reference range is 2 - 15 ng/mL.

Question 1: Should the dose be decreased by 50% to get the level closer to the lab reference range?

- What clinical information is needed to make this decision?
  1. Is there evidence of intolerability (e.g. EPS, akathisia)?
  2. Was the current dose arrived at systematically by exploring response at lower dosages?
Case: The Result

- Clinical data: no EPS or akathisia, and patient 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

Fluphenazine Decanoate: Single-Dose Pharmacokinetics

Fluphenazine Decanoate: Weekly Loading (50 mg/week)

Haloperidol Decanoate Loading

- The most aggressive depot haloperidol load permissible in California-DSH facilities is 300 mg weekly for 3 doses
- This regimen is designed to mimic plasma levels achievable with 30 mg/d of oral haloperidol.¹
- This dosing equivalency is an extrapolation of prior loading studies demonstrating that, after 3 weekly injections of haloperidol decanoate 100 mg, mean plasma haloperidol concentrations from the depot were comparable to 10 mg/d of oral haloperidol (7.95 ± 4.94 ng/mL vs. 7.79 ± 4.79 ng/mL).²

Case: High-Dose Fluphenazine

• 41-year-old man diagnosed with schizoaffective disorder, bipolar type on an involuntary medication order
  • multiple prior psychiatric inpatient hospitalizations and a 20-year violent criminal history.
• His current offense occurred while on probation for grabbing a paramedic’s genitals and destroying the inside of an ambulance after an overdose of prescription pills.
• Current offense relates to unprovoked threats toward a patron in line at a fast food restaurant.
  • He verbally threatened the patron and his family, then pulled out a box cutter.

Case: High-Dose Fluphenazine

Admission Mental Status Exam Findings:
• Speech extremely pressured, with flight of ideas.
• Perseverative, florid grandiose delusional ideation permeating all his responses.
• Thoughts disorganized with bizarre, religious, grandiose delusional content. “I’m supposed to be the Sun God, the Virgin Mary, Adam and Eve and the king of all kings.” “I died 5 times.”
• Daily auditory hallucinations of a Native American voice “guiding me” and telling him to “count numbers.”
• He believed he had female genitalia as well as male.
Case: High-Dose Fluphenazine: Initial Treatment Outcome

- Unsuccessful trial of quetiapine 800 mg/day combined first with lithium at increasing doses up to 1500 mg/d, and then a 6-week trial of adjunctive lamotrigine up to 200 mg
  - Remained aggressive, grandiose, hyperreligious and floridly psychotic
- Paliperidone palmitate was started with only brief unsustained improvement
- Olanzapine 20 mg/day started 2 months after admission and titrated to 60 mg/day over 2 weeks without improvement.

A Psychopharmacology Consultation was requested 3 months after admission. Recommendations:

- Replace paliperidone palmitate 234 mg with fluphenazine decanoate.
- Continue olanzapine 60 mg qhs.
- Lower lithium to 900 mg qhs since fluctuating levels indicated poor adherence.

Case: High-Dose Fluphenazine

3 months after admission:

- Fluphenazine decanoate replaced paliperidone palmitate
- Continued olanzapine 60 mg oral qhs
- After 2 months with slowly increasing doses of fluphenazine decanoate, the treating psychiatrist noted that delusional content decreased from nearly 100% to perhaps 50%.
  - At higher fluphenazine decanoate doses his plasma fluphenazine level was still relatively low.
- He was generally appropriate, but still had outbursts of loud agitated screaming.
Case: High-Dose Fluphenazine

<table>
<thead>
<tr>
<th>Date</th>
<th>Dose</th>
<th>Date</th>
<th>Dose</th>
<th>Date</th>
<th>Dose</th>
<th>Date</th>
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<th>Date</th>
<th>Dose</th>
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</thead>
<tbody>
<tr>
<td>2/26</td>
<td>25 mg</td>
<td>4/2</td>
<td>75 mg</td>
<td>5/13</td>
<td>75 mg</td>
<td>5/20</td>
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<td>150 mg</td>
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<td>5/26</td>
<td>75 mg</td>
<td></td>
<td></td>
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<tr>
<td>3/19</td>
<td>50 mg</td>
<td>4/29</td>
<td>150 mg</td>
<td>5/1</td>
<td>1.3 ng/mL</td>
<td>5/19</td>
<td>0.81 ng/mL</td>
<td>5/26</td>
<td>0.4 ng/mL</td>
<td></td>
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</tr>
<tr>
<td>3/26</td>
<td>75 mg</td>
<td>5/13</td>
<td>75 mg</td>
<td>4/17</td>
<td>0.83 ng/mL</td>
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Case: High-Dose Fluphenazine

- At fluphenazine decanoate dose of 100 mg IM every week his plasma level was still relatively low.
  - Continuing delusions, but these no longer predominated.
  - His thought content focused on reality issues and he was able to attend all therapy sessions without aggression.
- The attending psychiatrist estimated a 75% reduction in psychosis and a 100% reduction in aggression.
- Before the current hospitalization, his antipsychotics were not pushed up to a beneficial level.
  - Once the fluphenazine dose was increased he made major gains without notable side effects or concerning labs.
Olanzapine

Olanzapine Levels and D$_2$ Occupancy

Kapur S, et al. 5-HT2 and D2 receptor occupancy of olanzapine in schizophrenia: a PET investigation. Am J Psychiatry 1998; 155(7): 921-928
Depot Olanzapine Levels After Loading Remain ≤ 50 ng/mL

Upper Threshold for Response

There is probably an upper threshold beyond which the likelihood of response is poor versus the likelihood of leading to side effects:

- **Olanzapine** > 200 ng/mL

Comments:

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

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Case: Psychotic Violence Requiring High Dose Olanzapine

- 44 yo AA female with schizophrenia charged with arson and battery on olanzapine 50 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 1: Should the patient’s dose be decreased, given more time to respond, increased, or add a second antipsychotic?

Olanzapine - Answers

1. Wait more time?
   - The patient continues to be highly aggressive requiring regular PRN and restraint use. 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 the patients constipation. Levels of 120 ng/mL and possibly up to 200 ng/ml (if tolerated) are recommended to treat psychotic aggression.

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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Clozapine

Clozapine Does Not Achieve 80% $D_2$ Occupancy
Uchida H, et al. Predicting dopamine D2 receptor occupancy from plasma levels of antipsychotic drugs. J Clin Psychopharmacol 2011; 31: 318-325

Case: The Clozapine Nonresponder

- 37 yo white female with schizophrenia on clozapine 500 mg/d for 8 weeks with ongoing positive symptoms. Her plasma level is 723 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?
Question: What is the $D_2$ Occupancy for this Clozapine Plasma Level?

Answer: Who cares!

Uchida H, et al. Predicting dopamine D2 receptor occupancy from plasma levels of antipsychotic drugs. J Clin Psychopharmacol 2011; 31: 318-325

Clozapine - Answers

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, 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.

Upper Threshold for Response

- There is probably an upper threshold beyond which the likelihood of response is poor versus the likelihood of leading to side effects:
  - Clozapine: > 838 ng/mL \(^1\)

Comments:

- A recent review of violent forensic inpatients noted few additional responders to plasma clozapine levels > 1000 ng/ml. \(^2\)


Conclusions

- Plasma level is the best proxy we have for antipsychotic CNS action
- For those on oral medications dose is a poor predictor of plasma level due to adherence and kinetic issues
  - Obtaining plasma levels during periods of stability, especially in controlled circumstances, can help detect nonadherence
  - A working knowledge of dose-plasma level relationships for oral and depot medications can also help detect kinetic issues (e.g. CYP 2D6 ultrarapid metabolizers)
- For nonresponders, levels can help determine whether a point of futility has been reached, or whether further dose (& level) increases can be useful
- Laboratory reference ranges are idiosyncratic at best
  - Minimum response thresholds tend to be relatively accurate
  - The upper limits are based on average tolerability. Your patient may not be average and may both require and tolerate the high plasma level.