Understanding Pharmacokinetics in Psychiatry: An Advanced Primer for the Advanced Psychopharmacologist

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Practical “Take-Aways”

1. Why chose a specific formulation of a drug for a specific patient?
2. How pharmacokinetics differ among specific types of patients, such as the elderly, genetically defined populations, those with specific diseases, and those with surgical procedures, such as gastric bypass surgery.
3. How to use therapeutic drug monitoring to enhance the appropriate treatment of a patient.

3 Variables That Determine Drug Effect (ie, Clinical Response)

Clinical Response = 

Site(s) of action × Drug concentration at its site(s) of action × Patient’s biology

Affinity × Absorption × Genetics
Intrinsic Activity × Distribution × Age
Most Common Targets × Metabolism × Disease
Receptors × Elimination × Environment
Ion channels × (ADME) × (GADE)
Transporters × Enzymes

Case 1: “Sertraline-Resistant” Patient

34-year-old female with schizoaffective disorder

Current regimen: Haloperidol 4 mg/day and carbamazepine 1000 mg/day successfully stable for several years.

Develops a depressive episode and was started on sertraline 50 mg/day, which was gradually titrated to 200 mg/day over many weeks without success.

What would you do next? Is there any additional information that you would want to evaluate why she did not respond?

Case 2: “Sertraline-Sensitive” Patient

67-year-old female with recurrent major depressive disorder with positive family history.

Medical history was unremarkable and she was on no other medications. Her previous episode 10 years earlier had responded to nortriptyline 100 mg/day.

Her psychiatrist started sertraline 25 mg/day for the first week. By the second week, she was sufficiently improved that her psychiatrist did not advance the dose as originally planned. The next week, she was well.

Was she experiencing placebo response? How might you evaluate that possibility?

Case 3: Half-Life Supports Once-a-Day

37-year-old patient with schizoaffective disorder treated with:

- Thoridazine, 100 mg by mouth qid
- Phenytoin, 100 mg by mouth qid, and
- Amitriptyline, 50 mg by mouth qid

After stabilization, the patient complained of daytime sedation.

Hence, each drug was combined into a single bedtime dose.

The patient was found dead the next morning.

Why?
Case 4: Why a disconnect from half-life and duration of effect?

44-year-old patient with alcohol dependence presents to ED after 2 days of abstinence. He is disoriented, combative, and complaining of visual and tactile hallucinations. He had elevated heart rate, blood pressure, and temperature. Lorazepam was slowly administered IV. Within 15 minutes he was mildly sedated and was transferred to an inpatient unit.

That transfer took 30 to 45 minutes during which he received no additional lorazepam. When he arrived on the floor, his symptoms had returned and struck one of the nursing staff, and had to be restrained.

Given that lorazepam has a half-life of 8 to 10 hours, why had his symptoms returned?

Case 5: 66-year-old Male with MDD Presents with Dizziness

- 66-year-old male successfully treated for psychotic major depression with paroxetine, 40 mg/day, and liopendine, 24 mg/day administered once a day, and now on maintenance therapy.
- He develops bronchitis and his internist treats him with clarithromycin, 250 mg twice daily for 14 days. He comes for his routine psychiatric follow-up at the end of the first week of antibiotic therapy. He is doing well except for a couple of incidences of intermittent dizziness and an episode of near syncope.
- His comorbid medical conditions include type 2 diabetes mellitus well controlled with metformin, moderate obesity, and status post quadruple coronary bypass surgery 4 years ago.

What do you do?

Case 6: Disconnect between Serum Lithium Concentration and Clinical Toxicity

A 48-year-old female with bipolar I disorder had been stable on lithium, 1200 mg/day, for 6 months with plasma levels 0.8 – 1.0 mEq/L.

She developed a recurrence of her rheumatoid arthritis, for which her internist prescribed ibuprofen (800 mg tid).

A week later she was brought to the ED in a confused, disoriented, and lethargic state with ataxia and had periodic generalized myoclonic jerks. Lithium level was 4.0 mEq/L.

With dialysis, her lithium levels rapidly fell under 0.2 mEq/L but rapidly rebounded to over 3.0 mEq/L after discontinuation of dialysis.

Dialysis was restarted and continued with serum lithium dropping to non-detectable.

Nevertheless, her neurological status deteriorated and she died 5 days later.

What accounts for this disconnect?

For Psychiatric Drug Development, Target Proteins of Interest Have Fallen into 4 Major Classes

- Receptors are the targets of specific neurotransmitters
- Ion channels regulate the excitability of neurons
- Transporters ("uptake pumps") facilitate or inhibit the absorption of molecules into the body or specialized compartments (eg, brain)
- Enzymes synthesize or degrade specific chemical (eg, neurotransmitters)

The Question:

You are stranded alone on a tropical island.
You can only have one drug, an antidepressant.
Which one would you choose?
In Vitro Receptor Binding Affinity Profile of Quetiapine Expressed Relative to Its Most Potent Binding Site

Relative Binding Affinity

Quetiapine

Dopamine (D)
- D1
- D2
- D3

Others
- Histamine 1
- Muscarinic 1
- Alpha - NE 1
- Alpha 2

In Vitro Receptor Binding Affinity Profile of Quetiapine


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The Essence of Clinical Pharmacology

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Affinity × Intrinsic activity × PK Mechanisms

Absorption Distribution Metabolism Elimination (ADME)

PK = pharmacokinetic.


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Absorption Distribution Metabolism Elimination (ADME)

Age Disease Environment (GADE)

PK Mechanisms

Enzymes Transporters

Drug Administration Involves a Cascade of Events to Achieve Pharmacologic Effects

Oral dose GI tract Liver Clearance

Systemic circulation Peripheral distribution

Target organ Effect site Effect

GI = gastrointestinal.

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Pre-systemic Metabolism

Systemic circulation
Heart
Liver
Stomach
Gut wall
Metabolites

Drug Administration Involves a Cascade of Events to Achieve Pharmacologic Effects

Oral dose
Absorption & Distribution
Plasma concentration
Metabolism
Blood-brain barrier
CNS penetration
Target CNS receptors

CNS = central nervous system.

3 Sets of Intervening Factors from Dose to Effect

Drug dose
Intervening factors 1
Blood levels
Intervening factors 2
Brain levels
Intervening factors 3
Treatment response

Group I
Absorption
Distribution
Metabolism
Elimination

Group II
Bound-free ratio
Blood-brain barrier*
Cerebral blood flow*

Group III
Neurochemical variance (eg, receptor function, reuptake mechanisms, feedback systems)

Intervening Factors

*Most critical under non-steady-state conditions.

The Classic NIH Biogenic Amine Synapse

AMP = adenosine monophosphate;
ATP = adenosine triphosphate;
COMT = Catechol-O-methyltransferase;
MAO = monoamine oxidase.

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Percent Protein Bound is Not Generally a Mechanism for Meaningful PK DDI

The reason is because the issue is not how much of the drug is protein bound but instead whether the circulating protein binding sites are occupied.

Most of the drugs we use are in nanogram quantities and hence never come close to saturating the circulating protein binding sites.

To illustrate consider a parking lot.

The exception to this rule is valproate because its effective concentrations are in the microgram/mL (10–6) rather than in the nanogram/mL (10–9) range.

That illustrates how “weak” valproate is as a drug.

In fact, the beginning of the therapeutic range for valproate is 50 mcg/mL which is the concentration at which valproate generally has saturated its own binding sites and hence its free concentration increases exponentially rather than linearly as its concentration increase above 50 mcg/mL.

\[ % \text{ D}_2 \text{ Receptor Occupancy} \]

Relationship between D\textsubscript{2} Receptor Occupancy and D\textsubscript{2} Receptor Antagonist Concentration: Narrow Range between Efficacy and Behavioral Toxicity

\[ \text{Drug Concentration} \]

\[ \% \text{ Occupancy of D}_2 \text{ Receptors} \]

\[ \text{Threshold for antipsychotic efficacy} \]

\[ \text{Threshold for EPS} \]

Distribution Curves of % D\textsubscript{2} Occupancy as Function of Specific Doses of 2 Different Antipsychotics

\[ \text{Risperidone 6 mg qd} \]

\[ \text{Olanzapine 10 mg qd} \]

\[ \text{D}_{2} \text{ Receptor Occupancy in the Striatum} \]

\[ \text{Frequency} \]
Distribution Curves as a Function of Changing the Dose

5-HT Transporter Occupancy

Has been determined both in vitro using human platelets and in vivo using PET scanning.

Each SSRI and SNRI at its usually effective, minimum dose produces approximately 80% 5-HT occupancy.

Relationship between Dose, Usual Drug Level, Plasma Drug Level (Bound/Unbound), Kinetic Inhibition Rate Constant, and Magnitude of SE Uptake Inhibition in Platelets

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose (mg)</th>
<th>% protein bound</th>
<th>Free drug level (ng/mL)</th>
<th>Kinetic inhibition rate constant</th>
<th>SE uptake inhibition platelets</th>
</tr>
</thead>
<tbody>
<tr>
<td>Citalopram</td>
<td>40</td>
<td>85</td>
<td>50%</td>
<td>40</td>
<td>1.16</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>20</td>
<td>200</td>
<td>95%</td>
<td>10</td>
<td>0.83</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>20</td>
<td>40</td>
<td>95%</td>
<td>2</td>
<td>0.13</td>
</tr>
<tr>
<td>Venlafaxine</td>
<td>75</td>
<td>105</td>
<td>25%</td>
<td>75</td>
<td>9.09</td>
</tr>
</tbody>
</table>


Therapeutic Drug Monitoring

Results from Cases 1 and 2

<table>
<thead>
<tr>
<th>Case</th>
<th>Sertraline dose (mg/d)</th>
<th>Plasma level (ng/mL)</th>
<th>Time after dose (hrs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>200</td>
<td>17</td>
<td>12</td>
</tr>
<tr>
<td>2</td>
<td>25</td>
<td>28</td>
<td>12</td>
</tr>
</tbody>
</table>

Reference lab supplied the following data: Average steady-state peak plasma levels which occur 4.5 – 8.5 hours after a dose are:

<table>
<thead>
<tr>
<th>Dose (mg/d)</th>
<th>50</th>
<th>100</th>
<th>150</th>
<th>200</th>
</tr>
</thead>
<tbody>
<tr>
<td>Level (ng/mL)</td>
<td>32</td>
<td>84</td>
<td>144</td>
<td>190</td>
</tr>
</tbody>
</table>

The 3 Variables That Determine the Response to Any Drug

Clinical Response = Site(s) of action × Drug concentration at its site(s) of action × Patient’s biology

Absorption Genetics
Distribution Age
Metabolism Disease
Elimination Environment
(ADME) (GADE)

*(Adapted from Preskorn, SH. Clinical Pharmacology of Selective Serotonin Reuptake Inhibitors. Cadex, OK: Professional Communications, Inc; 1996.)*
Concentration

\[
\text{dosing rate} = \frac{\text{clearance}}{\text{concentration}} = \frac{\text{mg/min}}{\text{mL/min}}
\]

Relationship between Increase in Drug Exposure vs Decrease in Drug Clearance

Clinical Response =

Site(s) of action × Drug concentration at its site(s) of action × Underlying biology of the patient

Affinity
Intrinsic activity

Absorption
Distribution
Metabolism
Elimination (ADME)

Genetics
Age
Disease
Environment (GADE)

Drug Metabolism by the P450s


Time Course: Fluoxetine Effect on CYP 2D6


Time Course: CYP Enzyme Induction and Inhibition on Plasma Levels of a Substrate-Drug

CYP Enzymes Do Not “Take-over” for Each Other

The CYP450 System is an Integral Part of Phase I Drug Metabolism


Which #1 selling drug caused the death of 250 healthy young American women and why?
Oxidative Biotransformation of Terfenadine Metabolism in Humans


Time Needed to Attain Steady-State

The slope of the elimination phase is the measure of clearance? That is the reason why single-dose blood levels can be used to determine the dose of the drug needed in that patient to achieve the desired drug concentration.

What does “flip – flop” PK mean and what kind of forms of drugs does it apply to?

Depot medications principally antipsychotics in psychiatry.
"Flip-flop" PK refers to the fact that for these drugs the rate-limiting step in determining the concentration of the drug is absorption rather than elimination.

The same "flip-flop" PK but to a lesser extent applies to extended-release (ER) formulations. For this reason, ER formulations may not be appropriate for what kinds of patients?

Patients who have undergone gastric bypass surgery. The reason is that their transit time and the location in the bowel may not permit adequate absorption of the drug.

Goal of Therapeutic Drug Monitoring is to:

1. Determine the optimal dose for a given patient.
2. Determine whether nonadherence is the likely cause of suboptimal efficacy.

Why TCAs?
They Had a Narrow Therapeutic Index

Caveats on Therapeutic Drug Monitoring

- Plasma or serum concentration of a psychiatric drug is a surrogate (and an imperfect one) for the concentration at the site of action in the brain.
- Transporter proteins are important in keeping drugs out of the brain and they are polymorphic, too.
- Hence, the ratio of brain to plasma concentration may be different in a small but important subset of patients.