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Plasma Concentrations, Pharmacokinetics, and Their Clinical Relevance

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Understanding Pharmacokinetics is Important for Determining an Effective and Safe Treatment Plan

Provide an Overview of Pharmacokinetics (PK) and Pharmacodynamics (PD)

Describe the Differences in PK and Plasma Concentrations of Different Medication Formulations

Oral and Long-Acting Injectable (LAI)

Explain the Importance of PK and Plasma Concentrations in the Clinical Setting

Mayor S. *Prescriber*. 2017:28(3):45-48.

Pharmacokinetics vs Pharmacodynamics

Pharmacokinetics

- Study of how the drug is processed by the body[1,2]
  - **A**bsorption
  - **D**istribution
  - **M**etabolism
  - **E**limination

"What the body does to the drug"[1,3]

Pharmacodynamics

- Study of therapeutic effects of the drug on the body[4]
  - Relationship of drug concentration and drug response[4,5]
  - Drug action impacts therapeutic response and toxic effects[3,4]

"What the drug does to the body"[3,5]

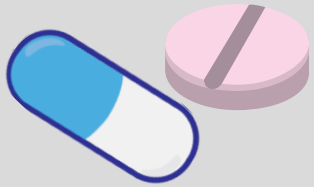
1. Currie GM. *J Nucl Med Technol.* 2018;46(3):221-230. 2. Correll CU, et al. *CNS Drugs.* 2021;35(1):39-59. 3. Newell DR. *Ann Oncol.* 1994;5 Suppl 4:9-15. 4. Jones AW. *WIREs Forensic Sci.* 2019;1(5):e1340.
5. Currie GM. *J Nucl Med Technol.* 2018;46(2):81-86.

Pharmacokinetics: Absorption

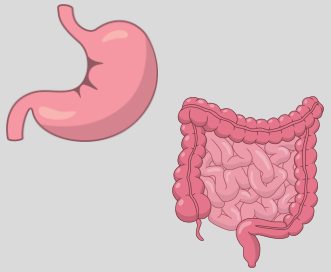
Drug is transported from site of drug administration to systemic circulation[1,2]

- **Bioavailability:** percentage of administered drug that reaches site of action[2]
- **Common routes of administration:**

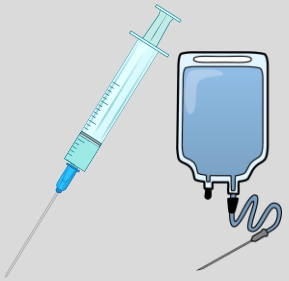
Oral

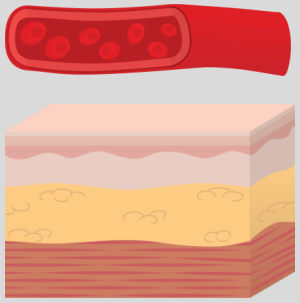


- Absorbed: stomach and intestines[1]
- **Bioavailability** can be reduced by first-pass metabolism[2]



Injection





← Intravenous

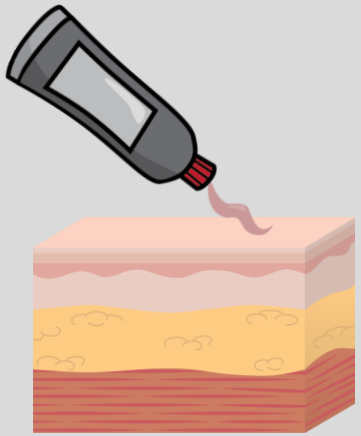
} **Bypasses absorption[1,2]**

← Subcutaneous
← Intramuscular

} **Slow absorption[2]**

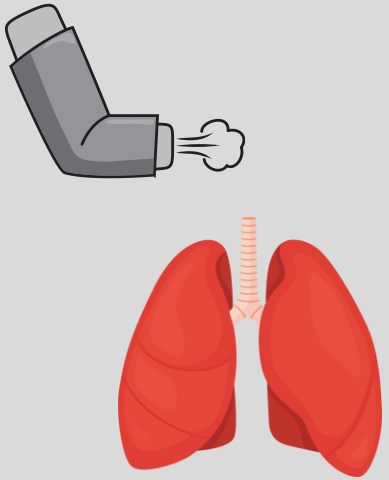
Topical

Absorbed by skin[1]



Inhalation

Absorbed in lungs[1]

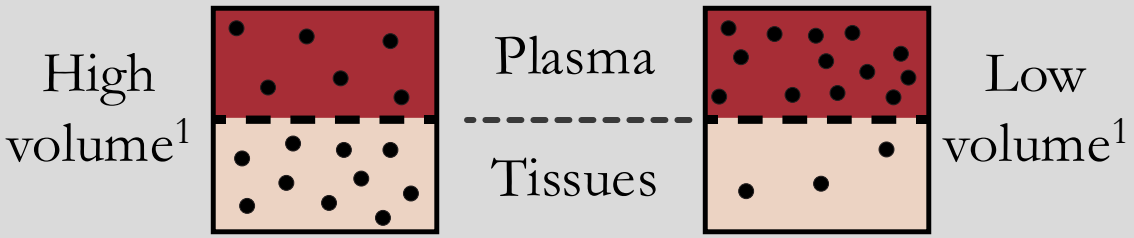


1. Alavijeh MS, et al. *NeuroRx*. 2005;2(4):554-571. 2. Currie GM. *J Nucl Med Technol*. 2018;46(3):221-230.

Pharmacokinetics: Distribution

Volume of distribution (VD)

- Describes the extent of distribution between plasma and tissues[1]
- Amount of drug in the body divided by drug plasma concentration[1,2]



Factors impacting VD

- Blood flow to tissue[1]
- Compartments (multiple tissues)[1,2]
- Plasma protein bound[1]
- Blood-brain barrier[1,3]

1. Currie GM. *J Nucl Med Technol.* 2018;46(3):221-230. 2. Alavijeh MS, et al. *NeuroRx.* 2005;2(4):554-571. 3. Banks WA. *BMC Neurol.* 2009;9:S3.

Pharmacokinetics: Metabolism

Drug structure is modified to facilitate elimination from body[1,2]

- Mostly done by enzymes in the liver (primarily cytochrome P450)[2,3]

Phases of metabolism[1]

Phase I

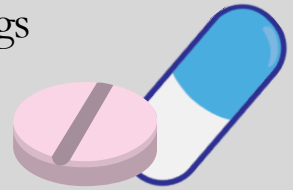
- **Reactions:** oxidation, reduction, and hydrolysis
- **Possible outcomes:**
  - Active drug is inactivated
  - Inactive drug form (prodrug) is activated

Phase II

- **Reactions:** conjugation and hydrolysis
- **Primary outcome:**
  - Attachment of a molecule to the drug that enables elimination

First-pass metabolism[1]

- Drug metabolism that occurs before drug reaches systemic circulation
- Lowers bioavailability
- Common for oral drugs



Factors impacting drug response

- Genetics[2,3]
- Age[1,4,5]
- Sex[2,5]
- Drug,[3] diet,[6] and lifestyle[6] interactions
- Disease impacting organ function[7]

1. Currie GM. *J Nucl Med Technol.* 2018;46(3):221-230. 2. Alavijeh MS, et al. *NeuroRx.* 2005;2(4):554-571. 3. Lynch T, et al. *Am Fam Physician.* 2007;76(3):391-396. 4. Mangoni AA, et al. *Br J Clin Pharmacol.* 2004;57(1):6-14. 5. Alomar MJ. *Saudi Pharm J.* 2014;22(2):83-94. 6. Niederberger E, et al. *Int J Mol Sci.* 2021;22(14):7692. 7. Staudinger JL. *Pharm Res.* 2013;30(9):2171-2173.

Pharmacokinetics: Elimination

Drugs are irreversibly removed from the body[1,2]

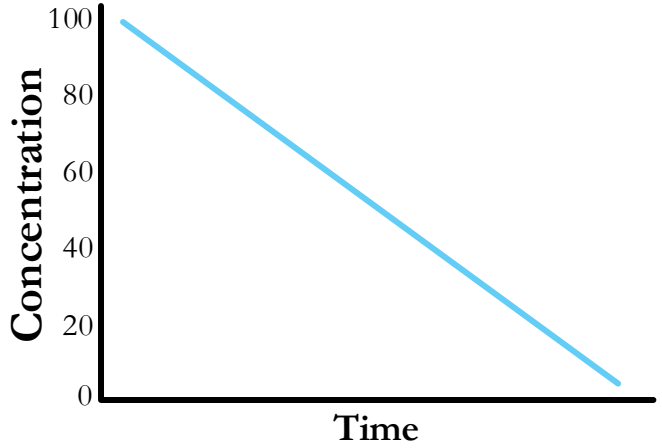
- Kidney filtration (urine) is the primary method[2,3]
- Elimination kinetics can be either zero- or first-order[2]
  - Most drugs are eliminated following first-order kinetics[1]

Elimination half-life ($t_{1/2}$)

Time it takes for 50% of drug to be eliminated[5]

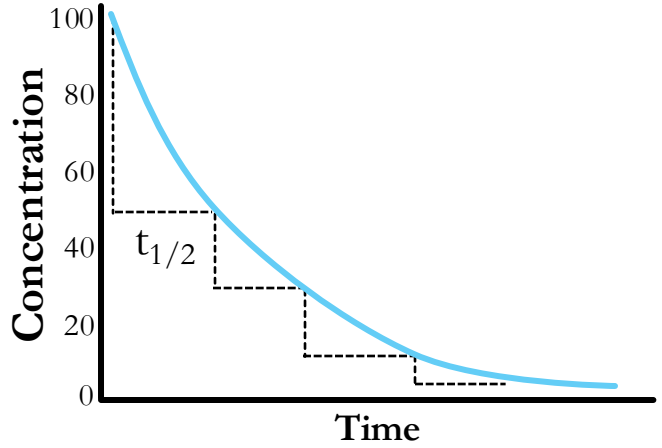
Zero-order

Constant **amount** of drug eliminated per unit of time[4]



First-order

Constant **fraction** of drug eliminated per unit of time[2,4]



Clinical relevance

- Values are used for[5,6]:
  - Estimating time to establish steady state
  - Estimating time to eliminate all of the drug

1. Jambhekar SS, et al. 1st ed. Pharmaceutical Press; 2009. 2. Currie GM. *J Nucl Med Technol.* 2018;46(3):221-230. 3. Alavijeh MS, et al. *NeuroRx.* 2005;2(4):554-571.
4. Jones AW. *WIREs Forensic Sci.* 2019;1(5):e1340. 5. Correll CU, et al. *CNS Drugs.* 2021;35(1):39-59. 6. Andrade C. *J Clin Psychiatry.* 2022;83(4):22f14584.

Pathway of Pharmacokinetics

Drug is administered

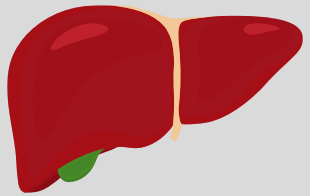
Absorption

Systemic circulation (blood plasma)

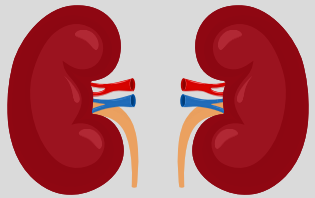
Drug exists as:
- Unbound drug
- Protein bound
- Modified forms

Distribution
- Drug reaches tissues and organs
- Site of action

Metabolism
- Enzymes modify drugs
- Typically inactivated
- Mostly done in liver



Elimination
- Drug leaves the body
- Primarily filtered at kidneys



Currie GM. *J Nucl Med Technol.* 2018;46(3):221-230.

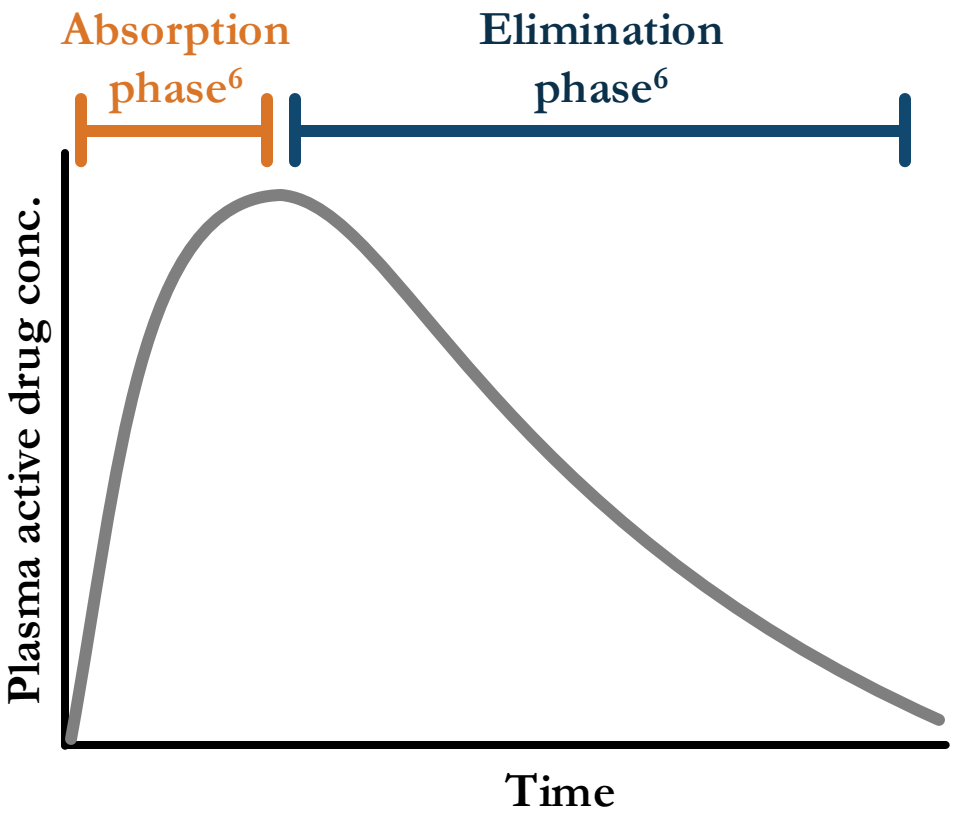
PK Data is Often Viewed as Drug Plasma Concentration Over Time[1]

Why use drug plasma concentration?

Drug efficacy is often determined by concentration at site of action[2,3]

Blood plasma concentration is used as an indirect measure[2]

Blood plasma concentration is often correlated to drug efficacy[2]



Clinical relevance

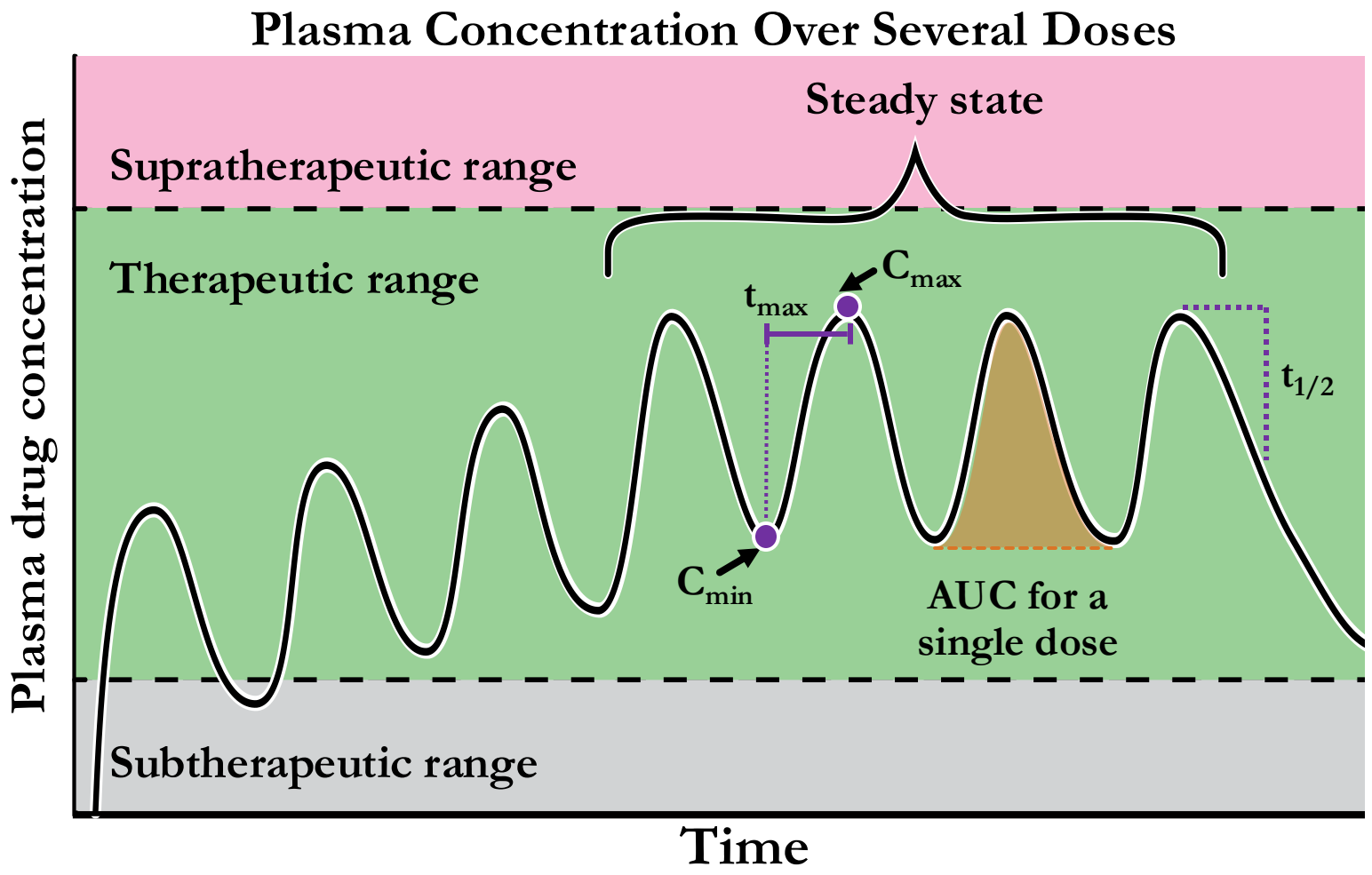
Drug plasma concentration is utilized to monitor therapeutic effect[4]

PK concepts are used to interpret drug plasma concentrations[4,5]

PK interpretations are utilized to optimize drug therapy (e.g., dosage adjustments)[4,5]

1. Jones AW. *WIREs Forensic Sci.* 2019;1(5):e1340. 2. Rizk ML, et al. *Clin Transl Sci.* 2017;10(3):133-142. 3. Currie GM. *J Nucl Med Technol.* 2018;46(2):81-86. 4. Kang JS, et al. *Korean J Intern Med.* 2009;24(1):1-10.
5. Correll CU, et al. *CNS Drugs.* 2021;35(1):39-59. 6. Jambhekar SS, et al. 1st ed. Pharmaceutical Press; 2009.

Understanding Pharmacokinetic Parameters



Terms[1-4]

Therapeutic range: plasma concentration range that produces therapeutic response[1]

C_{max}: maximal steady-state concentration[2]
- Extent of drug absorption[3]

t_{max}: time to C_{max}[2]
- Rate of drug absorption[3]

C_{min}: minimal steady-state concentration[2]

$t_{1/2}$: elimination half-life; time for 50% of drug to be eliminated[2]
- Correlates to drug action duration[4]
- Short half-life requires frequent doses[4]

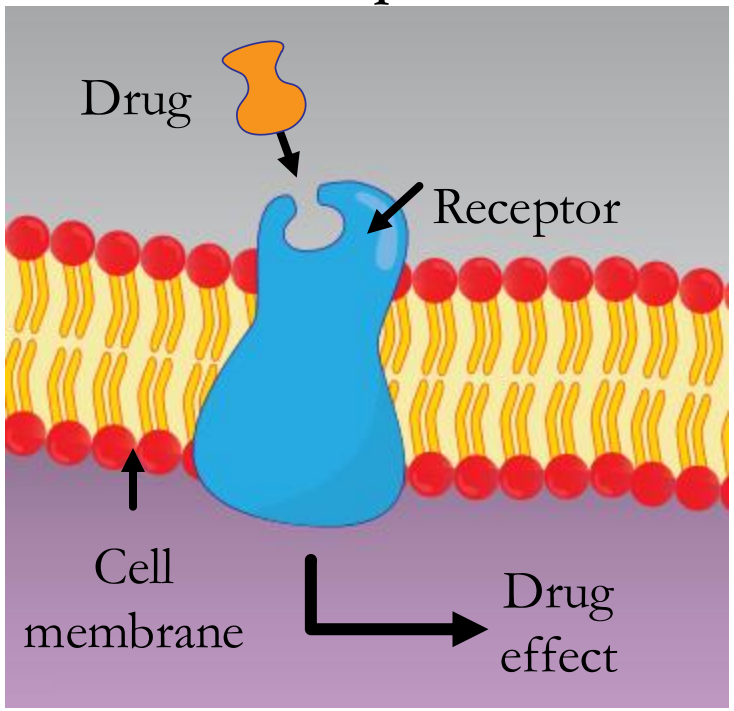
AUC: area under curve for dosing interval[2]
- Extent of drug exposure[3]
- Indicates elimination efficiency[3]

1. Currie GM. *J Nucl Med Technol.* 2018;46(3):221-230. 2. Correll CU, et al. *CNS Drugs.* 2021;35(1):39-59. 3. Urso R, et al. *Eur Rev Med Pharmacol Sci.* 2002;6(2-3):33-44. 4. Andrade C. *J Clin Psychiatry.* 2022;83(4):22f14584.

Pharmacodynamics (PD)

Drug action that is responsible for therapeutic response and toxic effects[1,2]

Action occurs when drug binds to receptors[3-5]



Drug action is determined by:

Affinity

- Strength of drug binding to specific receptor[3,5]
- High affinity typically requires lower dose[3]

Potency

- Relationship between drug dose and magnitude of the effect[3]
- High potency requires a low dose to produce a strong effect[3]

Efficacy (intrinsic activity)

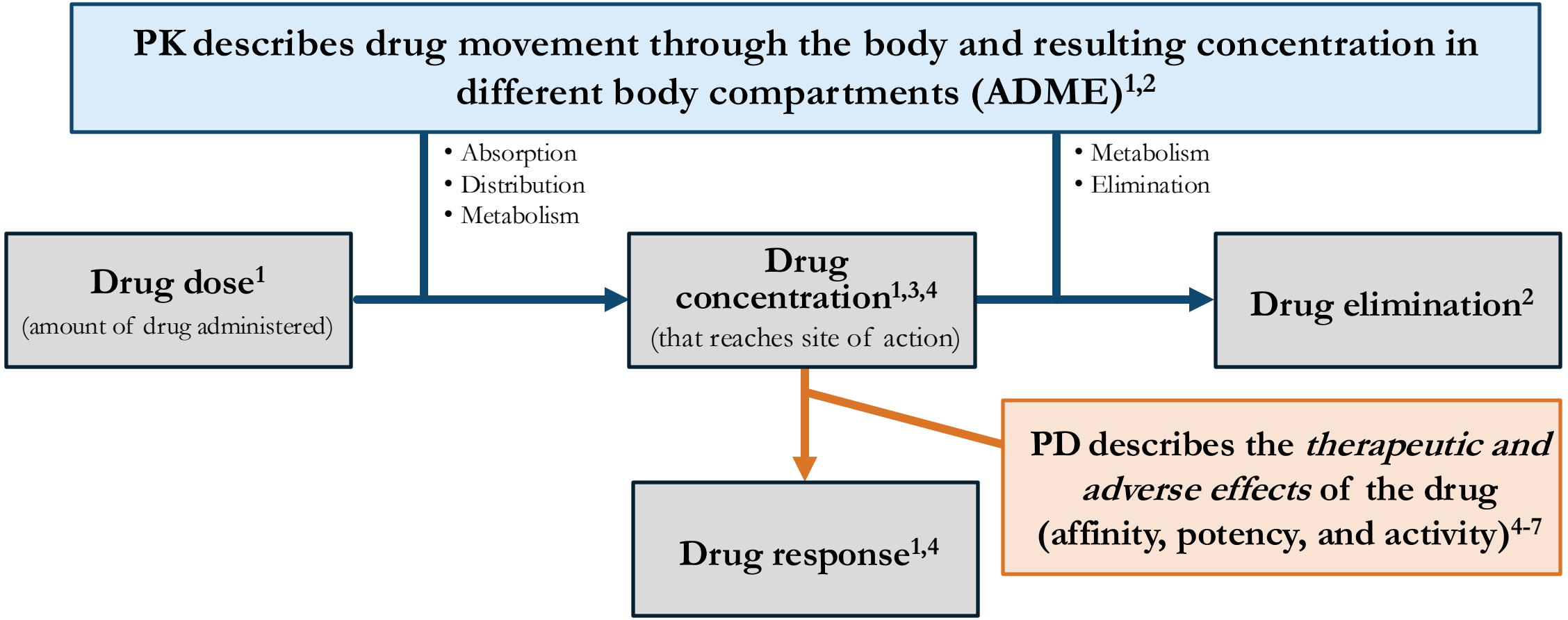
- Effect on receptor activity that leads to change in cellular activity[4,5]
- Relative measurement of ability to produce a response[4,5]

Clinical relevance

- Therapeutic effect is determined by concentration at site of action[6]
- Drug affinity, potency, and efficacy help determine required dose[3]

1. Newell DR. *Ann Oncol.* 1994;5 Suppl 4:9-15. 2. Jones AW. *WIREs Forensic Sci.* 2019;1(5):e1340. 3. Currie GM. *J Nucl Med Technol.* 2018;46(2):81-86. 4. Berg KA, et al. *Int J Neuropsychopharmacol.* 2018;21(10):962-977.
5. Salahudeen MS, et al. *Saudi Pharm J.* 2017;25(2):165-175. 6. Rizk ML, et al. *Clin Transl Sci.* 2017;10(3):133-142.

Connection Between PK and PD



1. Negus SS, et al. *Curr Top Behav Neurosci.* 2018;39:245-259. 2. Currie GM. *J Nucl Med Technol.* 2018;46(3):221-230. 3. Rizk ML, et al. *Clin Transl Sci.* 2017;10(3):133-142.
4. Salahudeen MS, et al. *Saudi Pharm J.* 2017;25(2):165-175. 5. Jones AW. *WIREs Forensic Sci.* 2019;1(5):e1340. 6. Newell DR. *Ann Oncol.* 1994;5 Suppl 4:9-15. 7. Currie GM. *J Nucl Med Technol.* 2018;46(2):81-86.

Apply Understanding of PK to Different Drug Formulations

Provide an Overview of Pharmacokinetics (PK) and Pharmacodynamics (PD)

☑ Completed

Describe the Differences in PK and Plasma Concentrations of Different Medication Formulations

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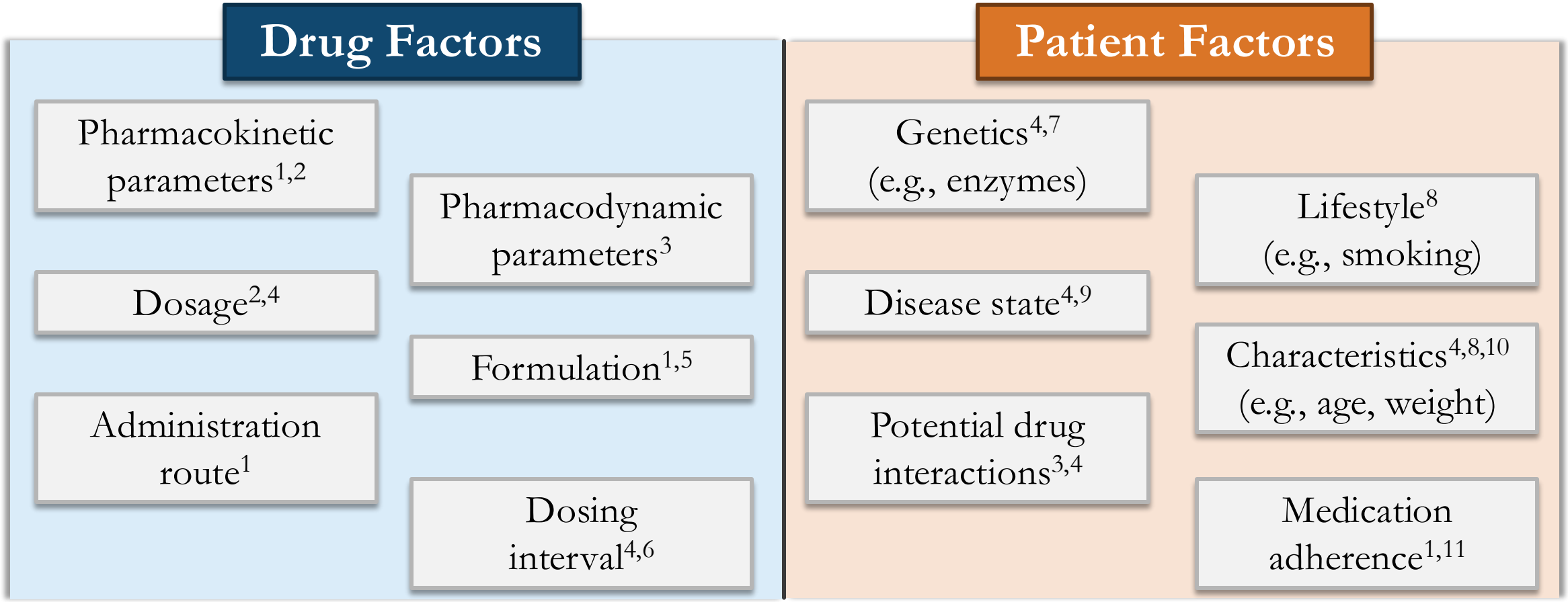
Oral and Long-Acting Injectable (LAI)

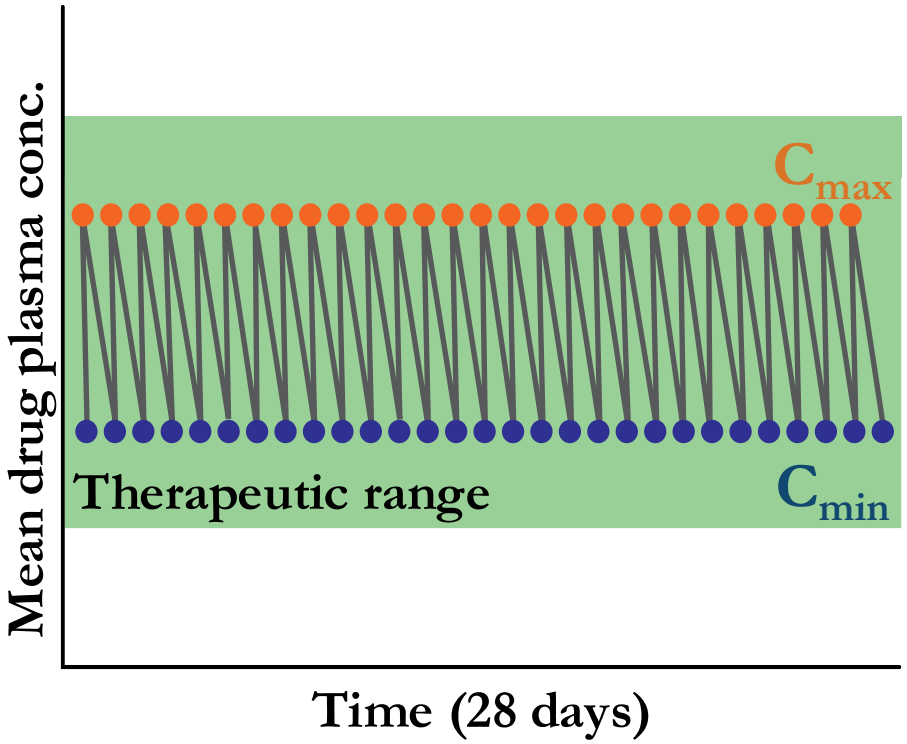
What Factors Determine Drug Effect?



1. Correll CU, et al. *CNS Drugs*. 2021;35(1):39-59. 2. Currie GM. *J Nucl Med Technol*. 2018;46(3):221-230. 3. Currie GM. *J Nucl Med Technol*. 2018;46(2):81-86. 4. Alomar MJ. *Saudi Pharm J*. 2014;22(2):83-94.
5. Chow SC. *Wiley Interdiscip Rev Comput Stat*. 2014;6(4):304-312. 6. Alavijeh MS, et al. *NeuroRx*. 2005;2(4):554-571. 7. Roden DM, et al. *Lancet*. 2019;394(10197):521-532. 8. Niederberger E, et al. *Int J Mol Sci*. 2021;22(14):7692.
9. Staudinger JL. *Pharm Res*. 2013;30(9):2171-2173. 10. Mangoni AA, et al. *Br J Clin Pharmacol*. 2004;57(1):6-14. 11. Levin JB, et al. *CNS Drugs*. 2016;30(9):819-835.

Differences in Dosing Interval and Administration Route Impact PK

Oral[1]



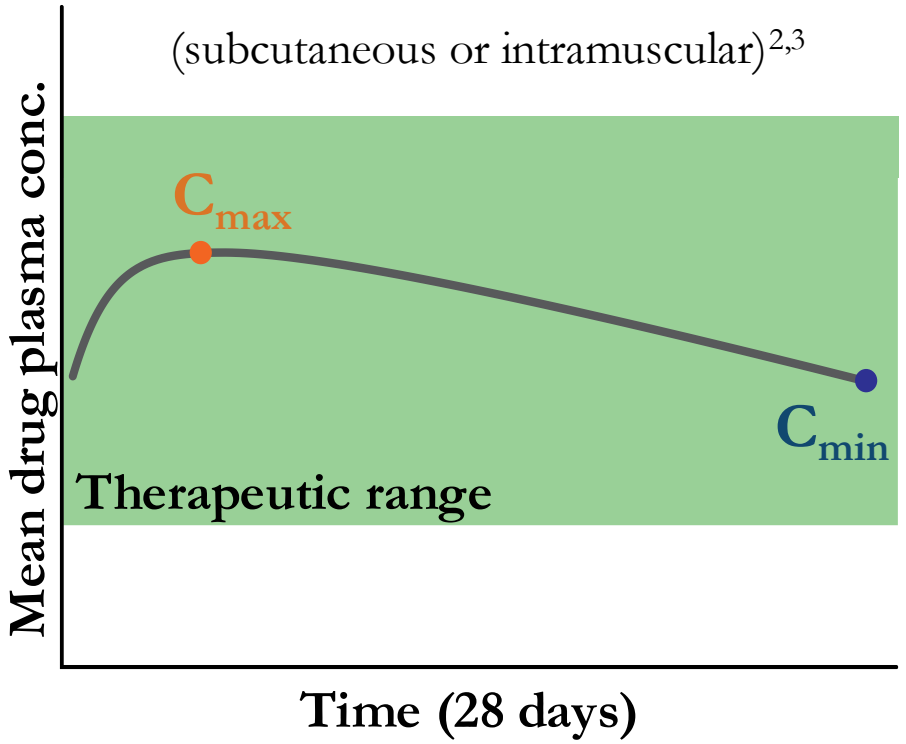
Dosing Interval[1,2]:

Daily or more frequent

Varies (every 2 weeks, monthly, etc)

Long-Acting Injectable (LAI)[1]

(subcutaneous or intramuscular)[2,3]



How do these differences affect PK and plasma concentrations?

1. Raoufinia A, et al. *Curr Med Res Opin.* 2015;31(3):583-592. 2. Hard ML, et al. *CNS Drugs.* 2017:31(7):617-624. 3. Correll CU, et al. *CNS Drugs.* 2021;35(1):39-59.

Key Differences in PK Between Oral and LAI Medications

Administration

Different dosing interval and administration route[1,2]

Oral

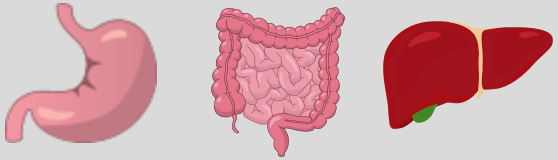
LAI

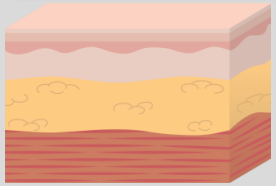
Absorption[2]

Rate and location affect time to maximal plasma concentration (t_{max})

Absorbed in GI tract

t_{max}: hours[3]





Subcutaneous

or

Intramuscular

Steady slow absorption[2]

t_{max}: days[3]

Metabolism[2]

Whether first-pass metabolism occurs affects bioavailability

First-pass metabolism lowers bioavailability[2,4]

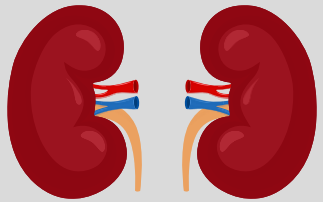
No first-pass metabolism[2,4]

- Less interpatient variability in bioavailability[5]

Distribution and Elimination

Once the drug is fully absorbed, these processes are relatively similar[2]

Complete elimination is extended due to slow *absorption* rate[2]



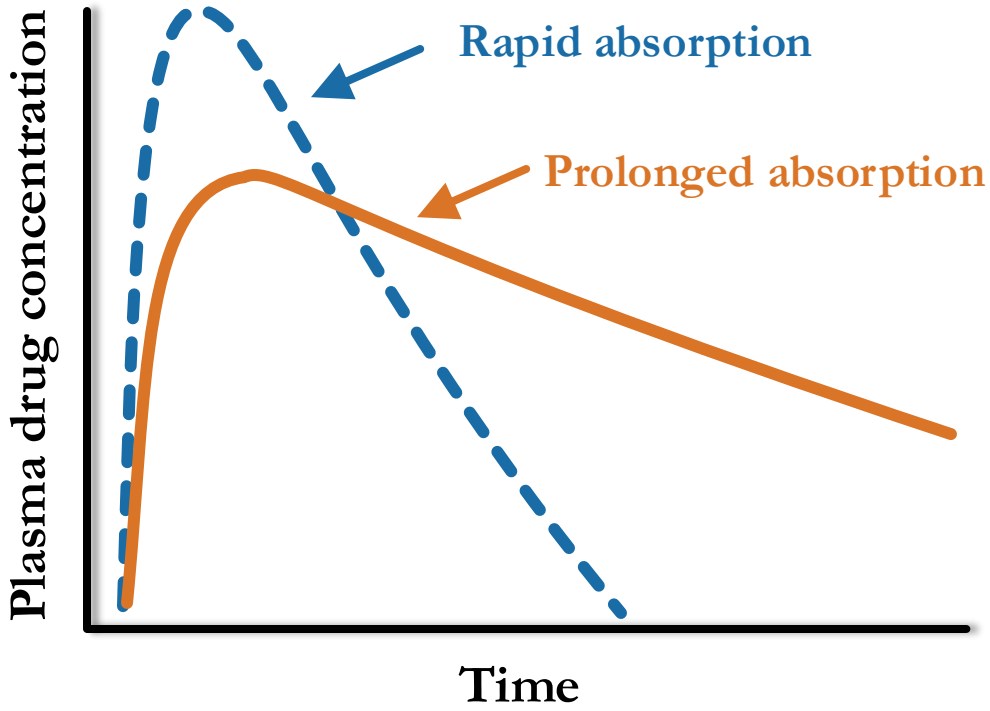
GI, gastrointestinal tract

1. Hard ML, et al. *CNS Drugs*. 2017:31(7):617-624. 2. Correll CU, et al. *CNS Drugs*. 2021;35(1):39-59. 3. Sheehan JJ, et al. *Innov Clin Neurosci*. 2012;9(7-8):17-23.
4. Currie GM. *J Nucl Med Technol*. 2018;46(3):221-230. 5. Kane JM, et al. *J Clin Epidemiol*. 2013;66(8 Suppl):S37-S41.

Slow Absorption Rate of LAIs Results in "Flip-flop" Kinetics

Flip-flop kinetics[1-3]

Absorption is slower than elimination



Impact and clinical relevance

- Absorption is the rate-limiting step[1,3]
- Elimination phase is slower and reflects the absorption rate[1,3]
- Apparent half-life[2]
  - Observed half-life for slow-release drugs[2]
  - Increased due to slow absorption[1,2]
- Drug half-life determines time to steady state and duration of drug action[2,4]

LAIs have flip-flop kinetics[2]

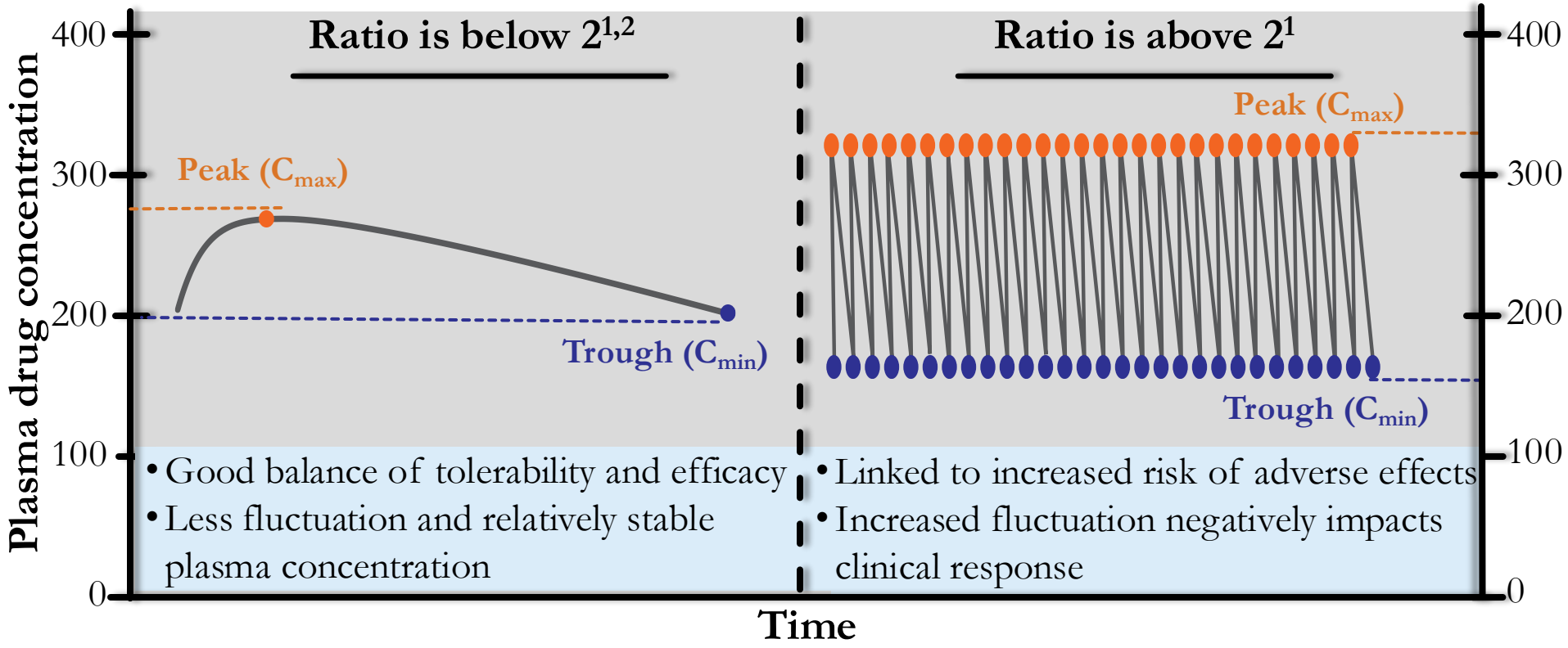
- Extended duration of drug plasma concentration and therapeutic effect[2]
- Long half-life requires less frequent doses[4,5]

1. Zou H, et al. *Front Pharmacol.* 2020;11:997. 2. Correll CU, et al. *CNS Drugs.* 2021;35(1):39-59. 3. Yáñez JA, et al. *Ther Deliv.* 2011;2(5):643-672. 4. Andrade C. *J Clin Psychiatry.* 2022;83(4):22f14584.
5. Alavijeh MS, et al. *NeuroRx.* 2005;2(4):554-571.

LAI Medications Have Low Peak-to-Trough Ratio

Peak-to-trough ratio: measurement of fluctuation[1,2]

- C_{max} (peak) divided by C_{min} (trough)



LAIs typically have low peak:trough[1,2]

- Slower absorption
- Longer t_{max}
- Long apparent half-life
- Stable plasma concentration

1. Correll CU, et al. *CNS Drugs*. 2021;35(1):39-59. 2. Sheehan JJ, et al. *Innov Clin Neurosci*. 2012;9(7-8):17-23.

Importance of PK and Plasma Concentrations in Clinical Setting

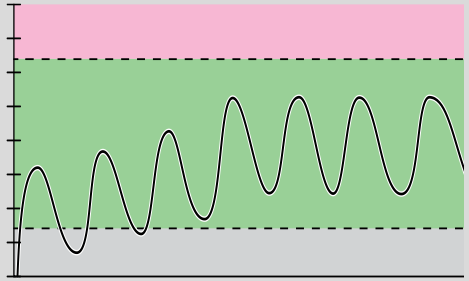
Describe the Differences in PK and Plasma Concentrations of Different Medication Formulations

Oral and Long-Acting Injectable (LAI)

Explain the Importance of PK and Plasma Concentrations in the Clinical Setting

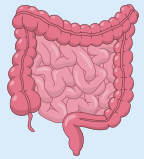
Clinical Relevance of PK

Desired drug effect is related to plasma concentration staying within therapeutic range[1]

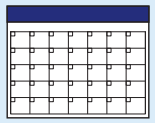


Understanding PK of drug formulations

Slow absorption[2-4]
- Extended drug exposure
- Less frequent doses required



Early metabolism[1,5]
- Lower bioavailability
- Higher dose may be required



Short half-life[4]
- Short drug exposure
- More frequent doses required

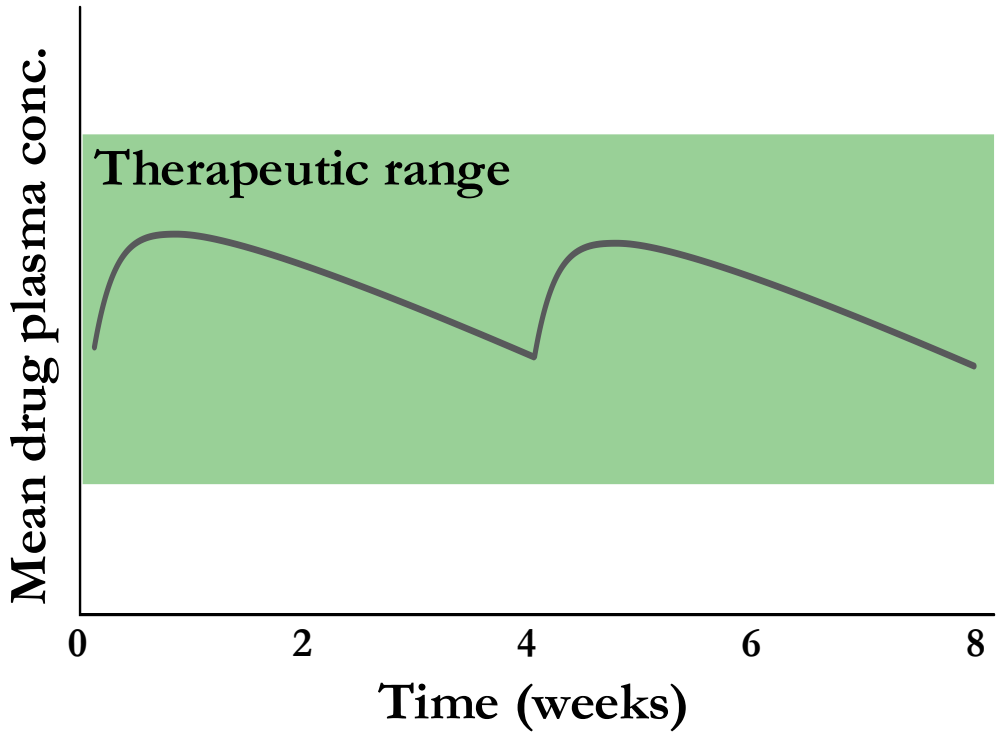
Understanding the variables (e.g., age,[6] genetics[7]) that affect PK is important for adjusting treatment regimens

PK data of new drug formulations can be compared to previously approved drugs to support bridging of efficacy

- Bioequivalence[8]
- PK bridging studies[9]

1. Currie GM. *J Nucl Med Technol*. 2018;46(3):221-230. 2. Correll CU, et al. *CNS Drugs*. 2021;35(1):39-59. 3. Alavijeh MS, et al. *NeuroRx*. 2005;2(4):554-571. 4. Andrade C. *J Clin Psychiatry*. 2022;83(4):22f14584.
5. Price G, et al. *StatPearls*. Accessed September 12, 2022. https://www.ncbi.nlm.nih.gov/books/NBK557852/ 6. Mangoni AA, et al. *Br J Clin Pharmacol*. 2004;57(1):6-14.
7. Roden DM, et al. *Lancet*. 2019;394(10197):521-532. 8. Chow SC. *Wiley Interdiscip Rev Comput Stat*. 2014;6(4):304-312. 9. Wang T, et al. *Transl Breast Cancer Res*. 2022;3:2.

Importance of Therapeutic Plasma Concentrations

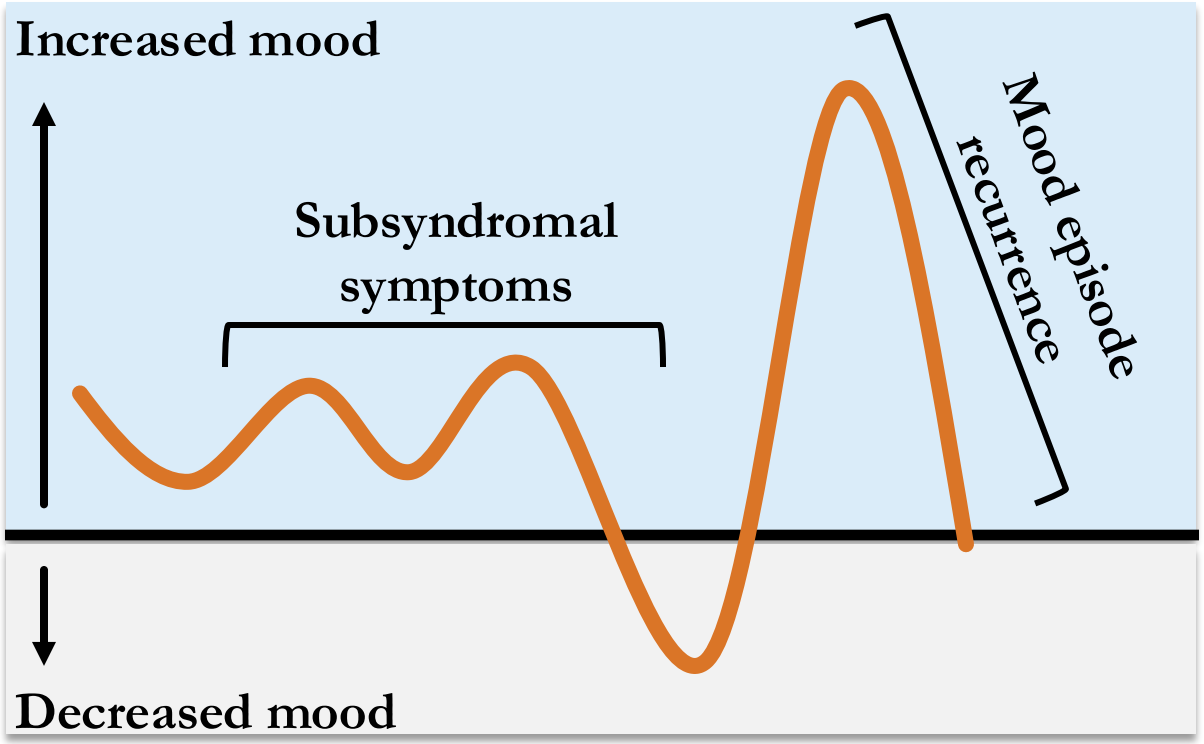


Efficacy[1,2]	Stabilized within established range for therapeutic effect
Safety[1,2]	Maintained within safe range to avoid adverse effects
Variability[3-6]	Individual characteristics can impact PK data (e.g., age,[3] genetics,[4] drug-drug interactions[5]) • Possible dose adjustments[6]
Consistency[6,7]	Stabilized plasma concentration is important for maintaining efficacy (e.g., symptom control)

1. Currie GM. *J Nucl Med Technol.* 2018;46(3):221-230. 2. Cooney L, et al. *BMC Med Res Methodol.* 2017;17(1):84. 3. Mangoni AA, et al. *Br J Clin Pharmacol.* 2004;57(1):6-14.
4. Roden DM, et al. *Lancet.* 2019;394(10197):521-532. 5. Currie GM. *J Nucl Med Technol.* 2018;46(2):81-86. 6. Correll CU, et al. *CNS Drugs.* 2021;35(1):39-59. 7. Hughes DA. *Br J Clin Pharmacol.* 2008;65(6):871-878.

Example of Clinical Relevance: Bipolar Disorder (BD)

BD is characterized by episodes of elevated and depressed mood[1]



Suggested goals of treatment[2]

Mood stabilization

- Returns patient with mania or depression back to stable mood

Maintenance

- Aims to prevent relapse events
- Reduces subsyndromal symptoms
- Enhances social and occupational functioning

Important factors

- Efficacy is dependent on maintaining drug plasma concentration within therapeutic window[3,4,5]
  - Maintain stable plasma concentration[6]
- Continuous treatment[5-7]

1. American Psychiatric Association. 5th ed, text revision. American Psychiatric Association; 2013. 2. Geddes JR, et al. *Lancet*. 2013;381(9878):1672-1682. 3. Currie GM. *J Nucl Med Technol*. 2018;46(3):221-230.
4. Cooney L, et al. *BMC Med Res Methodol*. 2017;17(1):84. 5. Wakamatsu A, et al. *Innov Clin Neurosci*. 2013;10(3):23-30. 6. Correll CU, et al. *CNS Drugs*. 2021;35(1):39-59. 7. Chakrabarti S. *World J Psychiatry*. 2016;6(4):399-409.

High Rate of Nonadherence in BD Patients

Up to 79%

Nonadherent with maintenance medicine[1,*]

Reasons for nonadherence

- Adverse side effects[2]
- Complex drug regimens[2]
- Financial cost[2]
- Attitude toward medication[2]
- Forgetting[2]
- Unclear instructions[2,3]
- Lack of illness understanding[3]

Consequences of nonadherence

- Increased risk of:
  - Relapse[2]
  - Mood episode recurrence[4]
    - Number of episodes is a moderator of brain changes and associated with neurocognitive decline[5]
  - Suicidality[4,6]
  - Subsyndromal symptoms[7]
  - Hospitalization[2]
- Decreased likelihood of recovery and remission[4,6]
- Treatment costs[2]

Pharmacokinetics

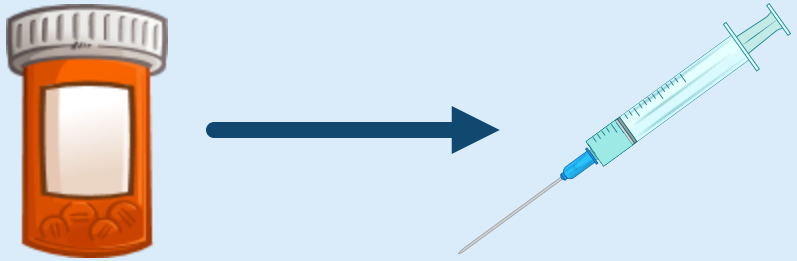
- Missed doses typically produce reduced and prolonged trough (C_{min}) concentrations[8]
- Potential loss of drug effect[8]

*In a retrospective claims-based study, ~79% of patients with bipolar disorder took antipsychotic medications less than 75% of the time.

1. Lage MJ, et al. *Ann Gen Psychiatry*. 2009;8:7. 2. Jawad I, et al. *Ther Adv Psychopharmacol*. 2018;8(12):349-363. 3. Hajda M, et al. *Neuropsychiatr Dis Treat*. 2016;12:1561-1570. 4. Levin JB, et al. *CNS Drugs*. 2016;30(9):819-835. 5. Kapczinski NS, et al. *Expert Rev Neurother*. 2017;17(3):277-285. 6. Hong J, et al. *Psychiatry Res*. 2011;190(1):110-114. 7. Montes JM, et al. *Patient Prefer Adherence*. 2013;7:89-94. 8. Hughes DA. *Br J Clin Pharmacol*. 2008;65(6):871-878.

LAIs May Offer a Solution to Nonadherence: Improved PK

LAIs were developed to overcome nonadherence with oral antipsychotics[1]



Improved pharmacokinetics

- LAIs ensure more consistent plasma levels via bypassing first-pass metabolism[2,3]
- Consistent dose delivery[1,4]
- Provide longer duration of pharmacological coverage[3,5]
- Missed dose does not decrease plasma concentration as rapidly as oral medications[6]

Clinical impact

- Delay time to mood episode recurrence in patients with bipolar I[7]
- May help with intentional and unintentional barriers to adherence[8]
- More time to intervene after missed dose[6]

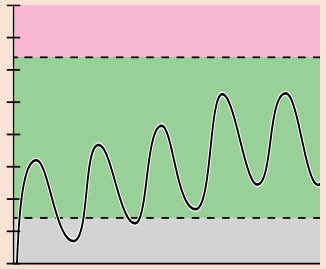
1. Tohen M, et al. *J Clin Psychiatry*. 2020;81(4):OT19046AH1. 2. Kane JM, et al. *Eur Neuropsychopharmacol*. 1998;8(1):55-66. 3. Keramatian K, et al. *CNS Drugs*. 2019;33(5):431-456.
4. El-Mallakh PL, et al. *Curr Drug Deliv*. 2013;10(6):706-712. 5. Correll CU, et al. *CNS Drugs*. 2021;35(1):39-59. 6. Kane JM, et al. *J Clin Epidemiol*. 2013;66(8 Suppl):S37-S41.
7. Macfadden W, et al. *Bipolar Disord*. 2009;11(8):827-839. 8. Levin JB, et al. *CNS Drugs*. 2016;30(9):819-835.

Summary

Pharmacokinetics (PK)[1,2]

"What the body does to the drug"

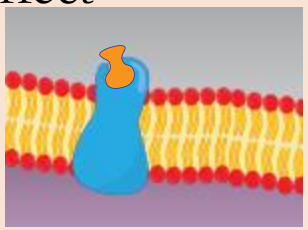
- **A**bsorption
- **D**istribution
- **M**etabolism
- **E**limination



Pharmacodynamics (PD)[2,3]

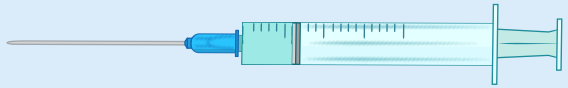
"What the drug does to the body"

- Drug therapeutic effect
- Affinity
- Potency
- Efficacy



LAIs offer sustained plasma concentrations over time[4-6]

- Slower absorption rate
  - Longer t_{max} (time to maximum concentration)
- Longer half-life
  - Increased duration of drug exposure and action
  - Less frequent doses required
- Low peak-to-trough ratio
  - Good balance of tolerability and efficacy



Importance of PK and plasma concentrations in the clinical setting

- Predictive of therapeutic effect and tolerability[4,7]
- LAIs maintain stable plasma drug concentrations[4]
- Changes to formulation will alter PK and thus drug plasma concentration[4,8]
  - Potential dose adjustments[4]

1. Currie GM. *J Nucl Med Technol*. 2018;46(3):221-230. 2. Newell DR. *Ann Oncol*. 1994;5 Suppl 4:9-15. 3. Salahudeen MS, et al. *Saudi Pharm J*. 2017;25(2):165-175. 4. Correll CU, et al. *CNS Drugs*. 2021;35(1):39-59.
5. Sheehan JJ, et al. *Innov Clin Neurosci*. 2012;9(7-8):17-23. 6. Andrade C. *J Clin Psychiatry*. 2022;83(4):22f14584. 7. Kang JS, et al. *Korean J Intern Med*. 2009;24(1):1-10.
8. Chow SC. *Wiley Interdiscip Rev Comput Stat*. 2014;6(4):304-312.

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Plasma Concentrations, Pharmacokinetics, and Their Clinical Relevance

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Back Up Slides

Pharmacokinetic (PK) Bridging Studies

PK bridging studies

- Enable extrapolation of PK data from previously approved drugs to support efficacy of changes[1]
  - e.g., dosage, administration route[1]
- Comparing bioavailability (AUC and C_{max}) determines bioequivalence[2]
  - Bioequivalence assumes same therapeutic effect is provided[2]
- Study design often uses models, simulations, and exposure-response analysis[3,4]
- PK studies and models have been used to determine the efficacy (therapeutic plasma concentration) of different LAI regimens[3,4]

Potential advantages[1]

Shortened timeline

Establish efficacy

- PK studies ensure drugs will work for new population or new suggested dose
- Genetic, physiological, and environmental differences could impact efficacy

Patient impact

- Reduces duplicate trials
- Reduces cost
- Drugs will be accessible much quicker

1. Wang T, et al. *Transl Breast Cancer Res.* 2022;3:2. 2. Chow SC. *Wiley Interdiscip Rev Comput Stat.* 2014;6(4):304-312. 3. Wang X, et al. *Clin Pharmacol Drug Dev.* 2022;11(2):150-164.
4. Hard ML, et al. *CNS Drugs.* 2017:31(7):617-624.