Advancing Kidney Health
Through Optimal Medication Management

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# Medication Regimen Design in Chronic Kidney Disease: A Primer on Pharmacokinetics

# How To Navigate the Module

- Glossary
- Additional Information PDFs
- Quizzes
- Websites
- Evaluation

# Glossary of Terms

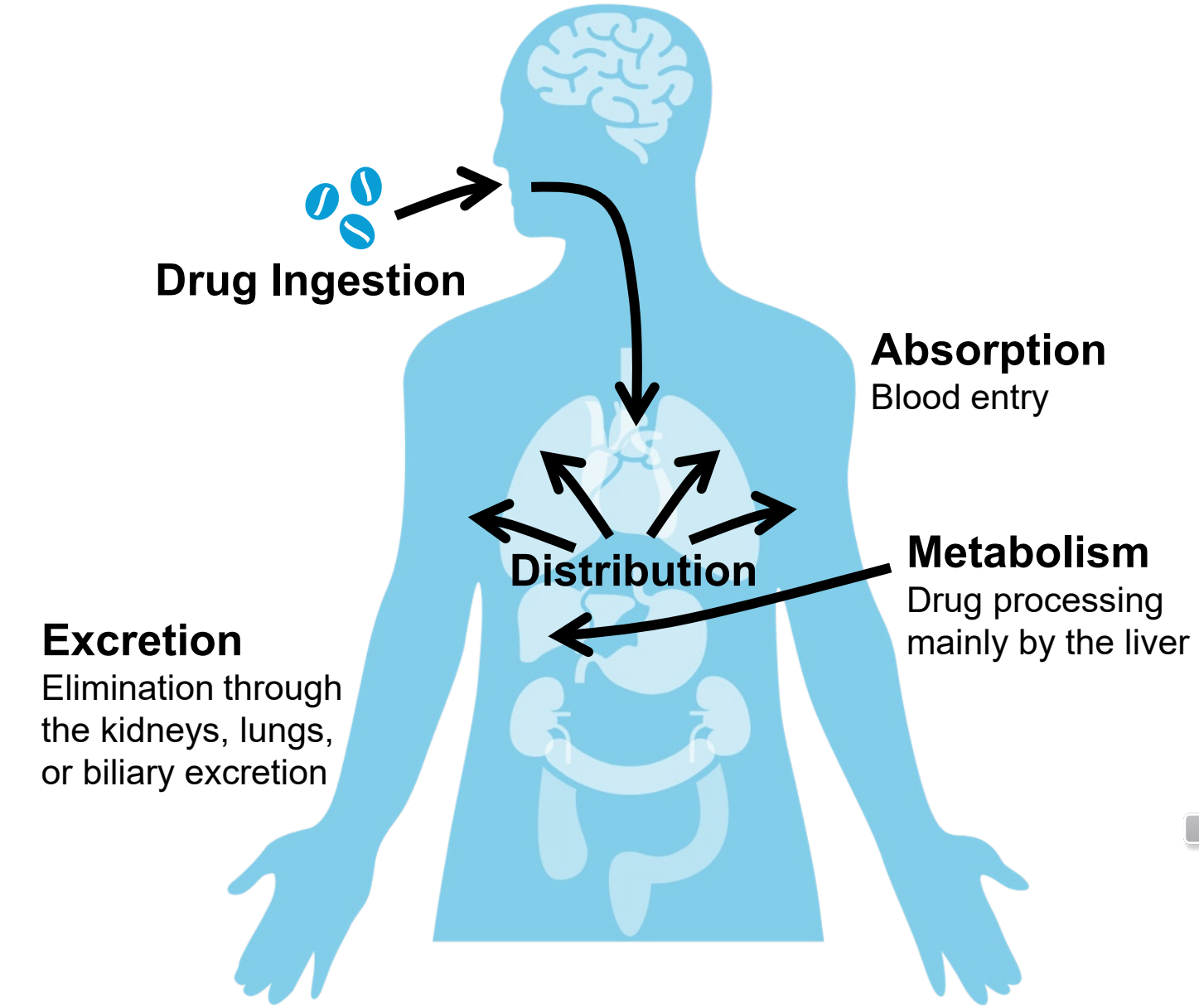

- **ADME** = absorption, distribution, metabolism, elimination
- **CKD** = chronic kidney disease
- **CKD-EPI** = Chronic Kidney Disease Epidemiology Collaboration
- **CL** = clearance
- **Css** = steady state concentration
- **eCrCL** = estimated creatinine clearance
- **eGFR** = estimated glomerular filtration rate
- **fe =** fraction of drug elimination by the kidney
- **fup =** fraction of drug unbound in plasma
- **GI** = Gastrointestinal
- **PD** = Pharmacodynamics
- **PG** = Pharmcogenomics
- **PK** = Pharmacokinetics
- **sCr** = serum creatinine
- **$t_{1/2}$** = half-life
- **$V_D$** = Volume of distribution

# What We Will Cover

- Clinically relevant changes in pharmacokinetics (PK) and pharmacodynamics (PD)
- Differentiating data derived from PK studies and outcomes studies
- Designing a dosing regimen and monitoring plan for high-risk medications
- Strategies to engage patients and caregivers

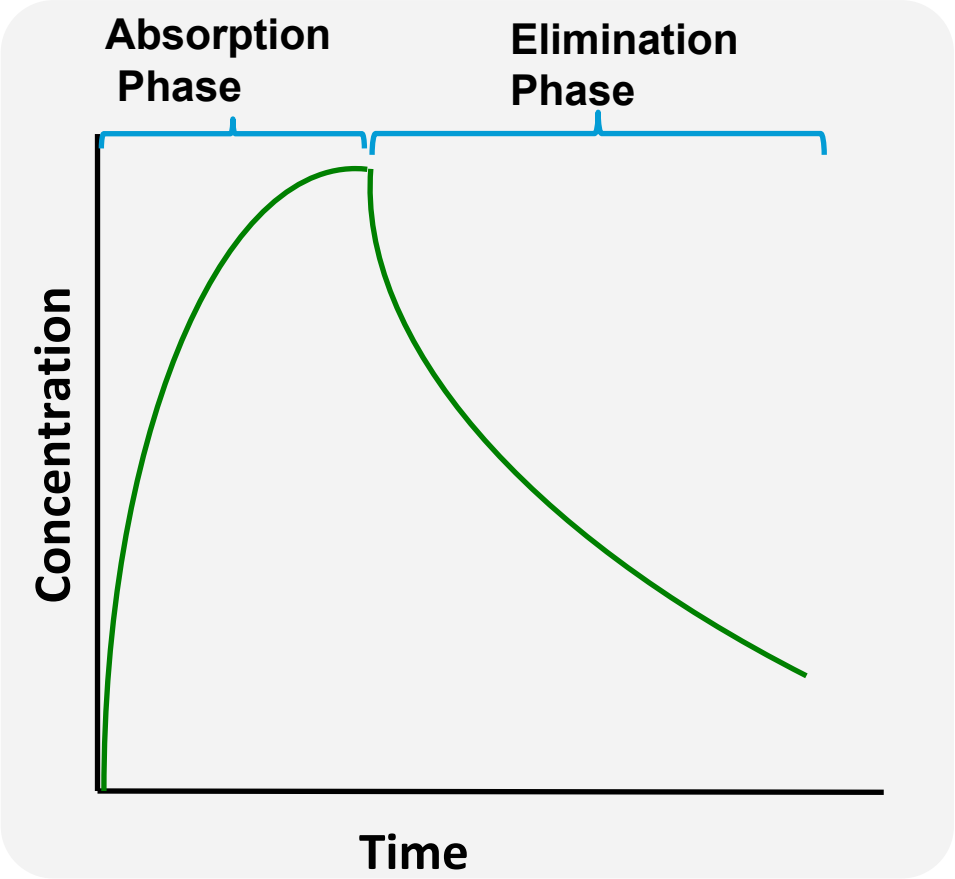
# What is Pharmacokinetics?

- **A** Absorption
- **D** Distribution
- **M** Metabolism
- **E** Elimination

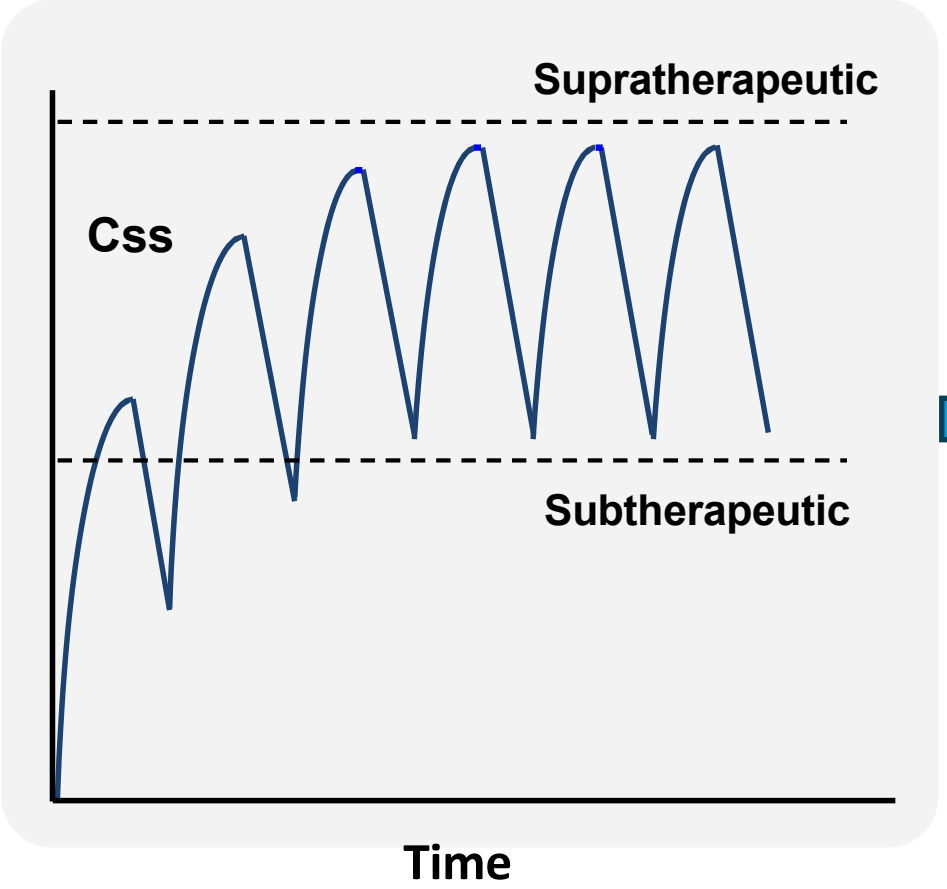


# Why is PK Important?

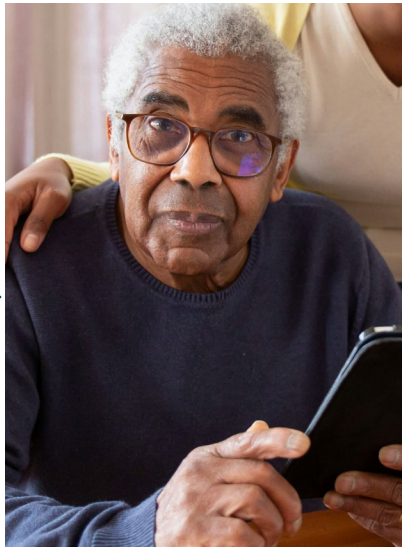
To design a safe and effective drug regimen for an individual




Single dose




Multiple doses

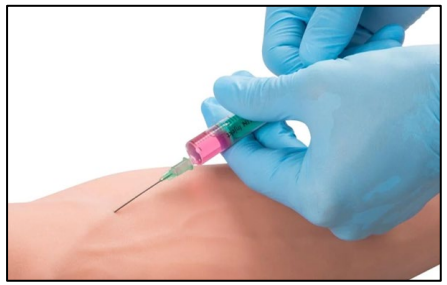


Desired PD effect for the patient

# A Absorption

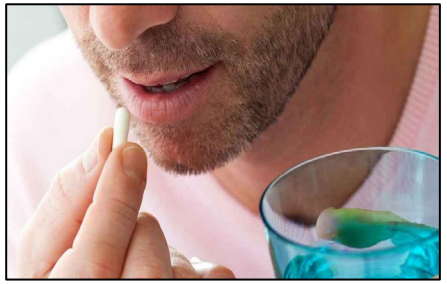
Movement of a drug from the site of administration to the systemic circulation.

*Bioavailability* indicates the percent of administered drug that gets absorbed.



**Intravenous administration**

100% bioavailability



**Oral administration**

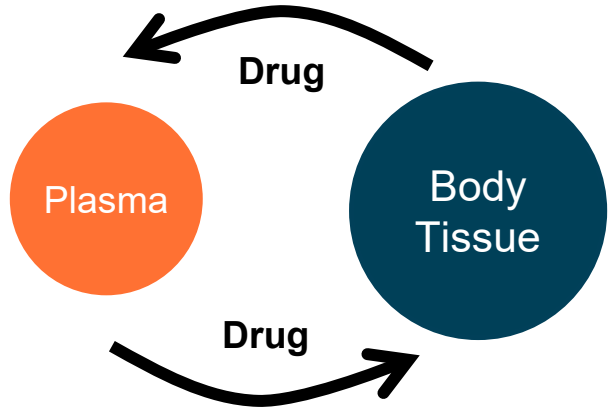
Bioavailability varies dependent on transit across the GI tract and the first pass effect (metabolism by the liver)

**Factors affecting GI absorption in CKD:**

- Changes in gastric pH
- Uremic gastritis
- Diabetic neuropathy
- Gut edema
- Drug interactions

# D Distribution

Disbursement of drug as it moves through the body; determines how much drug reaches the site of action.




- Described by the volume of distribution ($V_D$)

$$V_D = \frac{\text{Dose}}{\text{Plasma concentration}}$$

- $V_D$ is used to calculate a loading dose and gives an indication of how well a drug disperses throughout the body.
- Influenced by plasma protein binding, lipid solubility, and the blood-brain barrier.

**Factors affecting drug distribution in CKD**

Changes in protein binding

- ↓ Protein (e.g. albumin)
- Accumulation of uremic toxins displace drug from binding sites

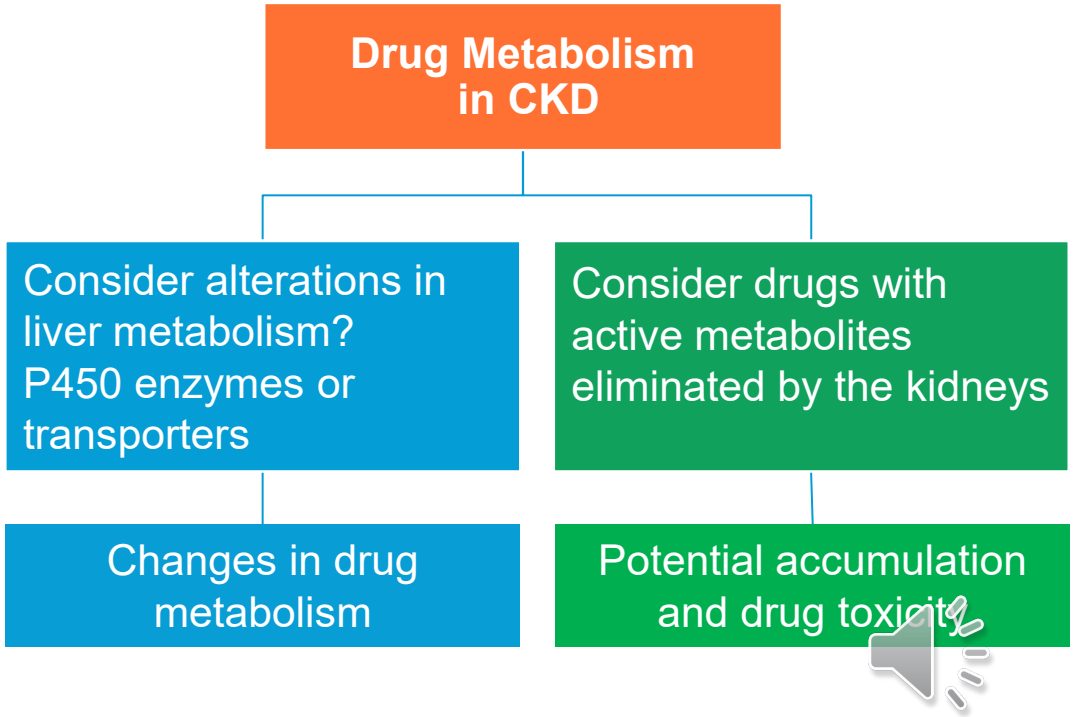
Volume overload

- Increased $V_D$ for hydrophilic drugs (e.g. gentamicin)

# M Metabolism

The biotransformation of drugs into different chemical forms (metabolites) in the body. These metabolites may be active or inactive.

- Some metabolism and drug degradation occurs within the kidney (e.g. gluconeogenesis; insulin degradation by cells in the proximal tubule).
- Most drug metabolism occurs in the liver by enzymes (cytochrome P450 and transferase enzymes) that cause phase I and phase II reactions to create metabolites (active or inactive) and facilitate drug elimination.
- Individual drug metabolism rates are influenced by genetic factors, comorbid conditions and drug interactions.



# Examples of Drugs with Active Metabolites Eliminated by the Kidneys

| Parent Drug | Active Metabolite | Potential Adverse Effect |
|---|---|---|
| **Allopurinol** | Oxypurinol | Increased risk of all reported general and life-threatening ADRs (e.g. aplastic anemia, thrombocytopenia) |
| **Diazepam** | Oxazepam | Sedation |
| **Meperidine** | Normeperidine | Seizures |
| **Midazolam** | Alpha-hydroxymidazolam | CNS effects |
| **Morphine** | Morphine-6-glucuronide | CNS effects |
| **Nitroprusside** | Thiocyanate | Cyanide toxicity |
| **Procainamide** | N-acetylprocainamide (NAPA) | Arrhythmia |

# Pharmacogenomics

- *Pharmacogenomics* refers to the branch of genetics concerned with the way in which an individual's genetic attributes affect the likely response to drugs.
- Pharmacogenetic testing may be done for individuals requiring drugs dependent on these particular metabolic enzymes.
- The Clinical Pharmacogenetics Implementation Consortium (CPIC) is an international consortium providing gene/drug clinical practice guidelines to help translate genetic laboratory test results into prescribing decisions for affected drugs.
- More information is available at CPIC (cpicpgx.org).

# E Elimination

Removal of a drug from the body, either in its unchanged form or as a metabolite. Overall elimination is the sum of non-kidney clearance and kidney clearance.

Kidney clearance ($CL_{Kidney}$) represents the volume of plasma cleared of solutes (or drug) via elimination by the kidney per unit of time.

$$CL_{Kidney} = \frac{\text{rate of elimination}}{\text{plasma concentration}}$$

$$CL_{Kidney}\ X = \frac{(\text{urine concentration of X}) \times (\text{urine flow rate})}{\text{plasma concentration of X}}$$

fe is the fraction of drug eliminated by the kidney and ranges from 0-1.

$$fe = \frac{CL_{Kidney}}{CL_{Total}}$$

Half-life ($t_{1/2}$) is the amount of time required for the plasma drug concentration to decrease by one-half.

$$t_{1/2} = \frac{0.693}{\text{elimination rate constant or ke}}$$

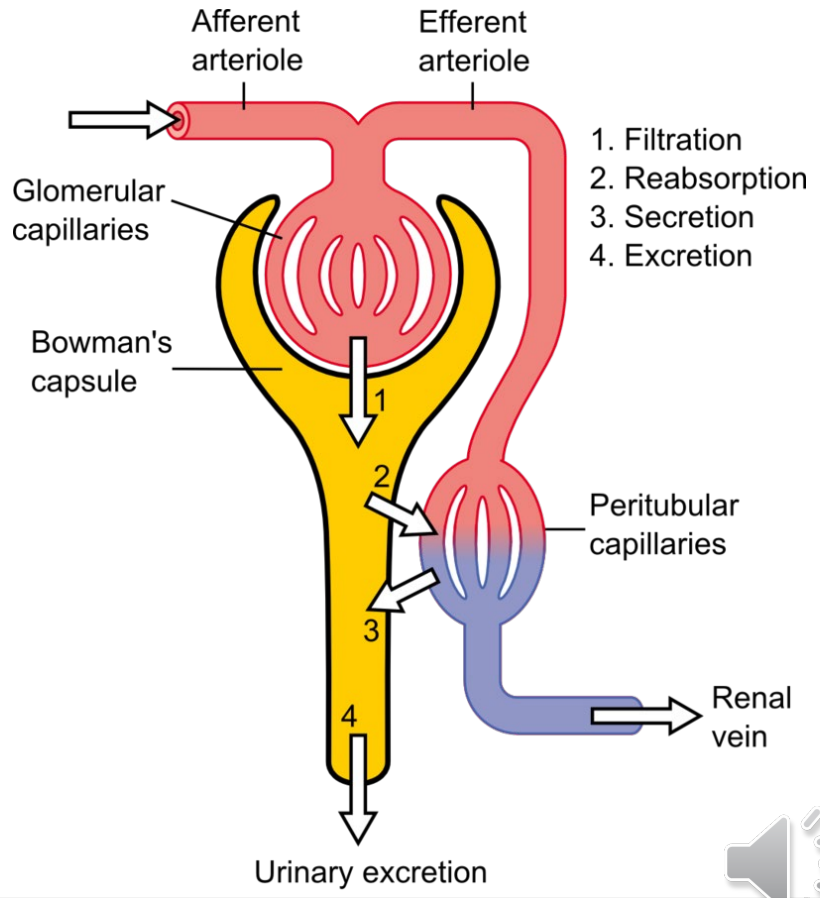
# E Processes of Urinary Excretion

1. Glomerular filtration

   Drugs not bound to plasma proteins or formed elements in the blood (e.g. red blood cells) will be filtered at the glomerulus if not prohibited by molecular size.

2. Tubular Reabsorption
   - Some substances filtered at the glomerulus are reabsorbed by passive diffusion depending on the ionization of the drug and urinary pH.
   - Active reabsorption may also occur for a relatively small number of drugs.

3. Tubular Secretion
   - Many drugs do not enter the glomerular filtrate but are transported into the lumen by tubular secretion.
   - Drugs bound to plasma proteins may be secreted by these active secretory systems.




**Kidney clearance = Glomerular filtration + Tubular secretion - Tubular reabsorption**

# Clearance Ratio

The net process a drug undergoes can be determined by calculating the ***Clearance Ratio*** ($CL_{ratio}$):

$$CL_{ratio} = \frac{CL_{Kidney}}{CL_{filtration}} = \frac{CL_{Kidney}}{fup \times 125\ mL/min}$$

$CL_{ratio} < 1.0$: the drug is filtered and undergoes net reabsorption. This does not mean that secretion did not occur.

$CL_{ratio} = 1.0$: the drug is filtered *and* reabsorption = secretion, or f reabsorbed = 0 and $CL_{secretion} = 0$.

$CL_{ratio} > 1.0$: the drug is filtered and undergoes net secretion.

fup = fraction of unbound drug in the plasma

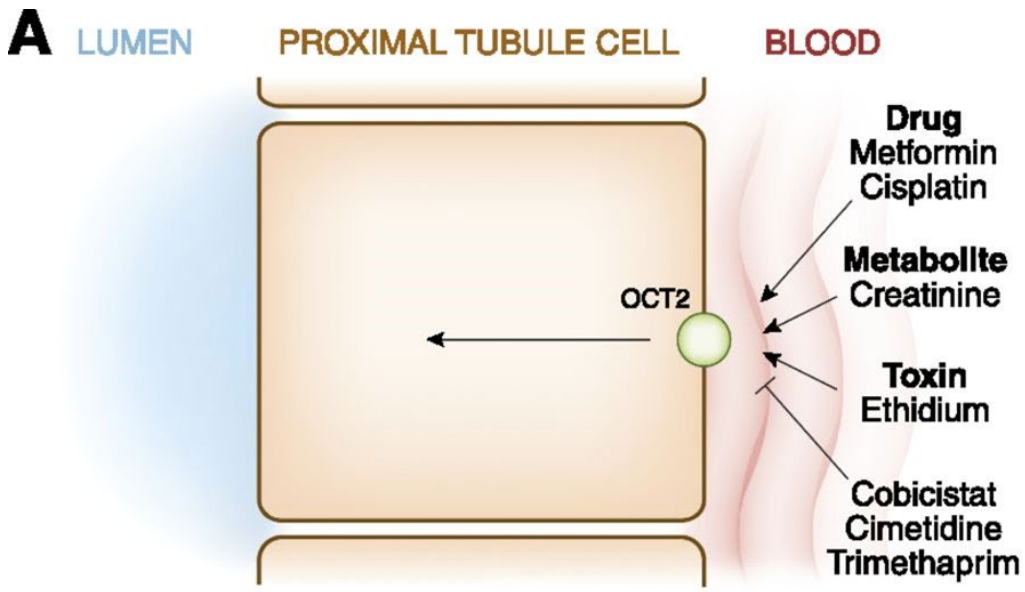
# Examples Showing Drugs with Net Reabsorption and Secretion

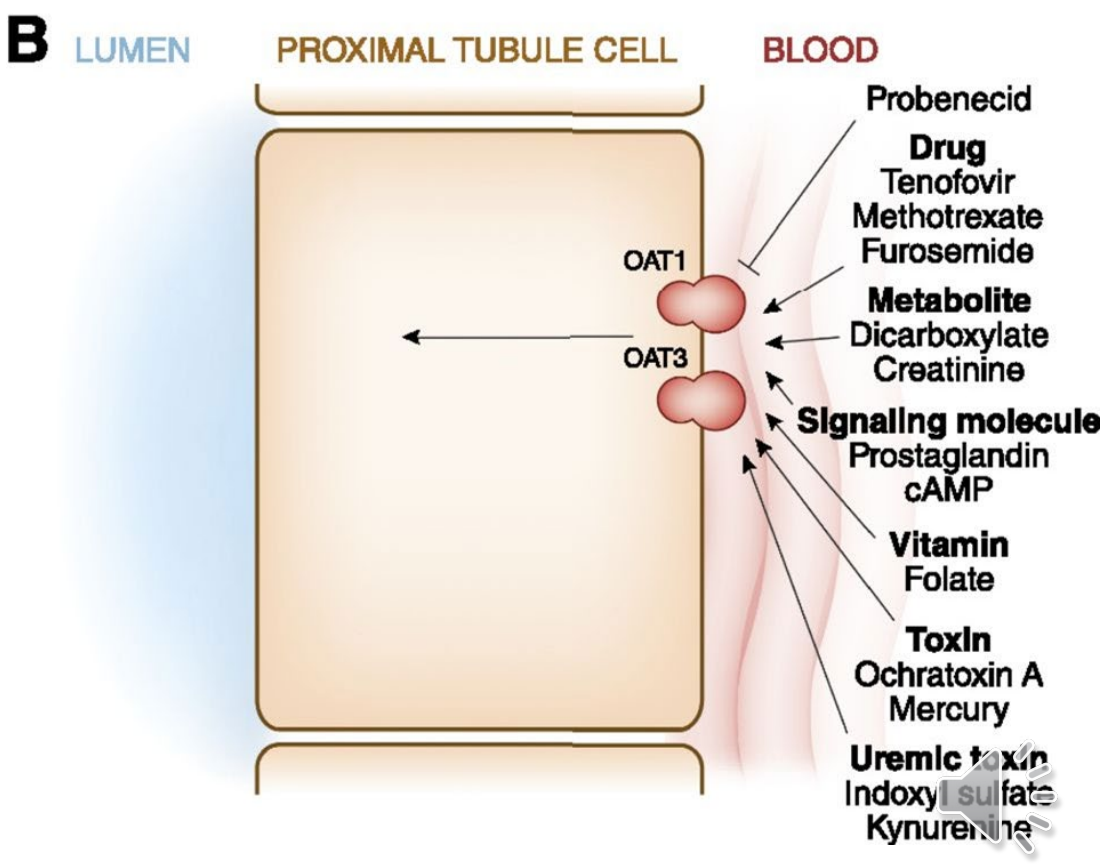
| Drug | *CL | fe | *CLkidney | fup | CLratio | Net |
|---|---|---|---|---|---|---|
| Gentamicin | 85 | 1.0 | 85 | 1.0 | .68 | R |
| Theophylline | 50 | .01 | 5 | 0.5 | .08 | R |
| Digoxin | 190 | 0.68 | 129 | 0.75 | 1.4 | S |
| Procainamide | 1000 | 0.5 | 500 | 0.85 | 4.7 | S |
| Lidocaine | 1000 | 0.02 | 20 | 0.2 | 0.8 | R |
| Cimetidine | 500 | 0.8 | 400 | 0.8 | 4.0 | S |

*CL expressed in mL/min/70kg

R=reabsorption; S=secretion; NA = not applicable

# Schematic of potential interactions between drugs, metabolites, and toxins due to competition for tubular secretion at the transporter level.




OCT = organic cation transporters
OAT = organic anion transporters

Image: Sanjay K. Nigam et al. CJASN 2015;10:2039-2049

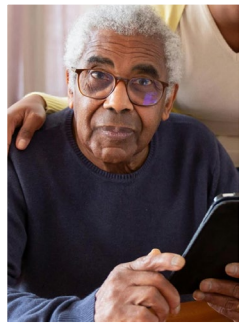
# What do we do with PK information to help the patient with CKD?

Consider alterations in drug regimen to account for PK changes and identify potential drug interactions….

Make necessary changes and educate the patient about their drug regimen.

Increase the likelihood that a medication will be safe and effective for the patient.

# Case Study



**Patient**

RT is a 72-year-old, 89 kg male (Ht 6'2") who resides at home with his wife who is disabled

Allergies: NKDA

| Labs/Vitals | Today | 6 mos ago |
|---|---|---|
| A1c (%) | | 6.5 |
| K (mEq/L) | 4.9 | 4.5 |
| SCr (mg/dL) | 2.4 | 2.4 |
| eGFR (mL/min/1.73 $m^2$) | 28 | 28 |
| $eGFR_{BSAadj}$ (mL/min) | 35 | 35 |
| UACR (mg/g) | 340 | 420 |
| Blood Pressure | 134/74 | 142/82 |

| PMH | |
|---|---|
| DM2 with neuropathy | Bipolar disorder |
| Atrial fibrillation | Seizure disorder |
| Chronic Kidney Disease Stage 3b | Osteoarthritis |

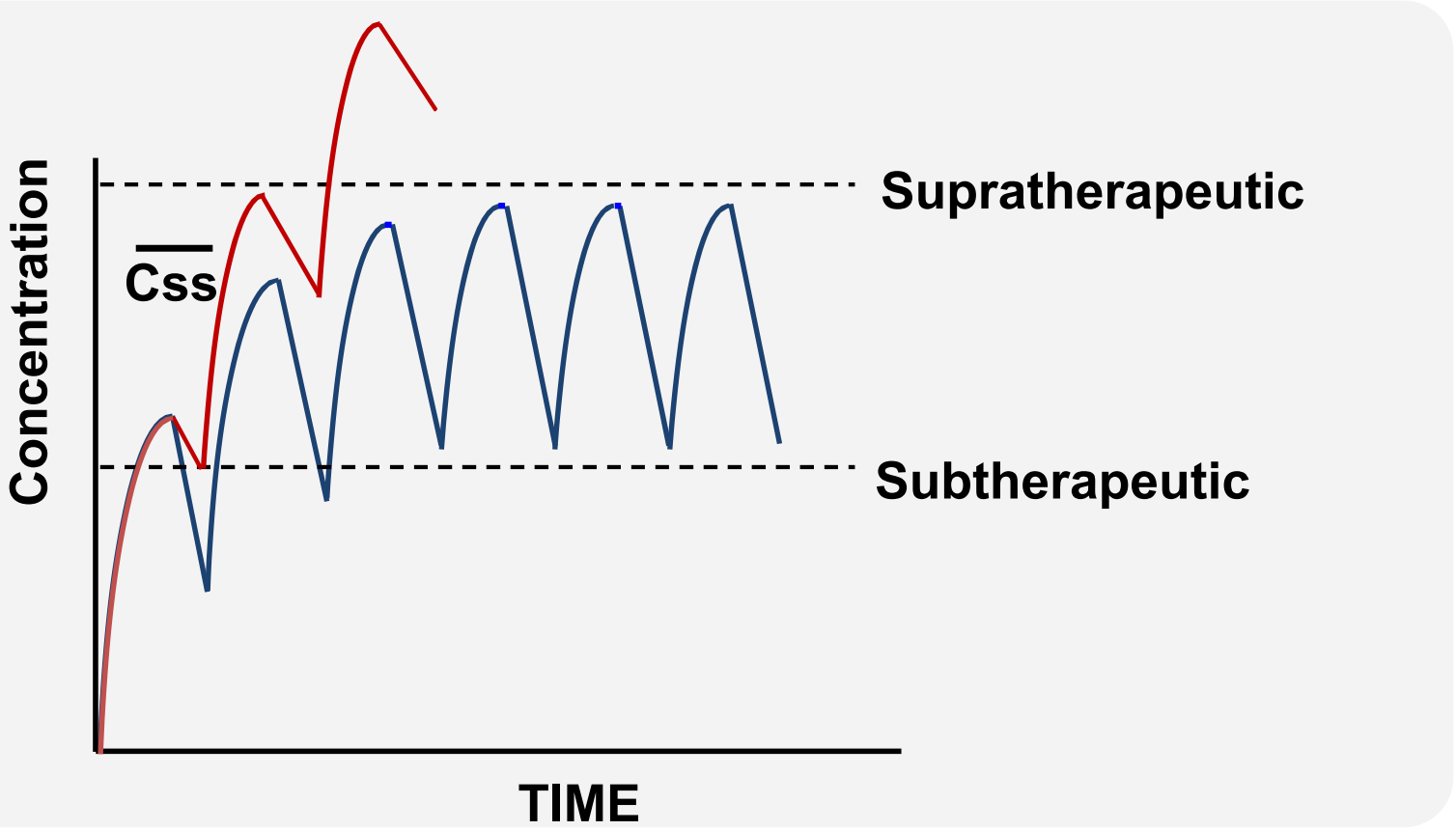
| Medications |
|---|
| Acetaminophen 500 – 1000 mg PO PRN arthritis |
| Apixaban 5 mg PO BID |
| Atorvastatin 40 mg PO daily |
| Dapagliflozin 10 mg PO daily |
| Gabapentin 600 mg PO TID |
| Levetiracetam 1000 mg PO BID |
| Lisinopril 40 mg PO daily |
| Lithium 600 mg PO TID |
| Metformin 1000 mg PO BID |

# Terminology

| Suggested Terminology | Units | Abbreviation | Other Terminology |
|---|---|---|---|
| Standardized eGFR | mL/min/1.73m$^2$ | eGFR | Indexed eGFR |
| eGFR adjusted for individual's body surface area (BSA) | mL/min | $eGFR_{BSAadj}$ | Non-indexed eGFR, De-indexed eGFR |

# Concentration Versus Time Profile (Drug with fe=1)

***Same dose and dosing interval***




**Drug administered IV over 30 minutes**

***Assume the $V_D$ is the same**

**Blue: Normal kidney function**

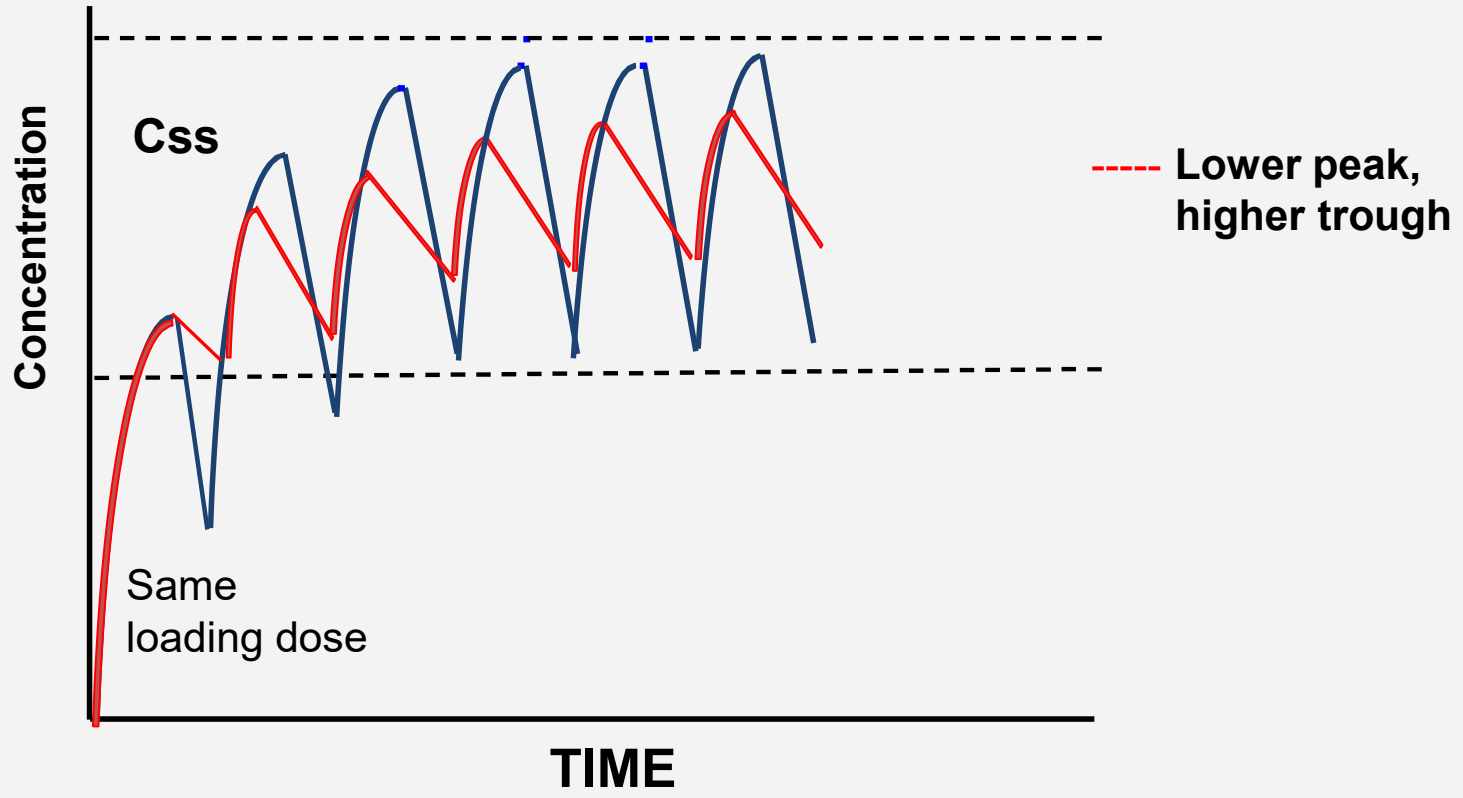
**Red: Reduced kidney function**

***Dashed lines represent the upper and lower drug level of the therapeutic range.***

fe = fraction eliminated by the kidney

# Concentration Versus Time Profile with Normal and Reduced Kidney Function

## *Reduced Dose with Same Dosing Interval*

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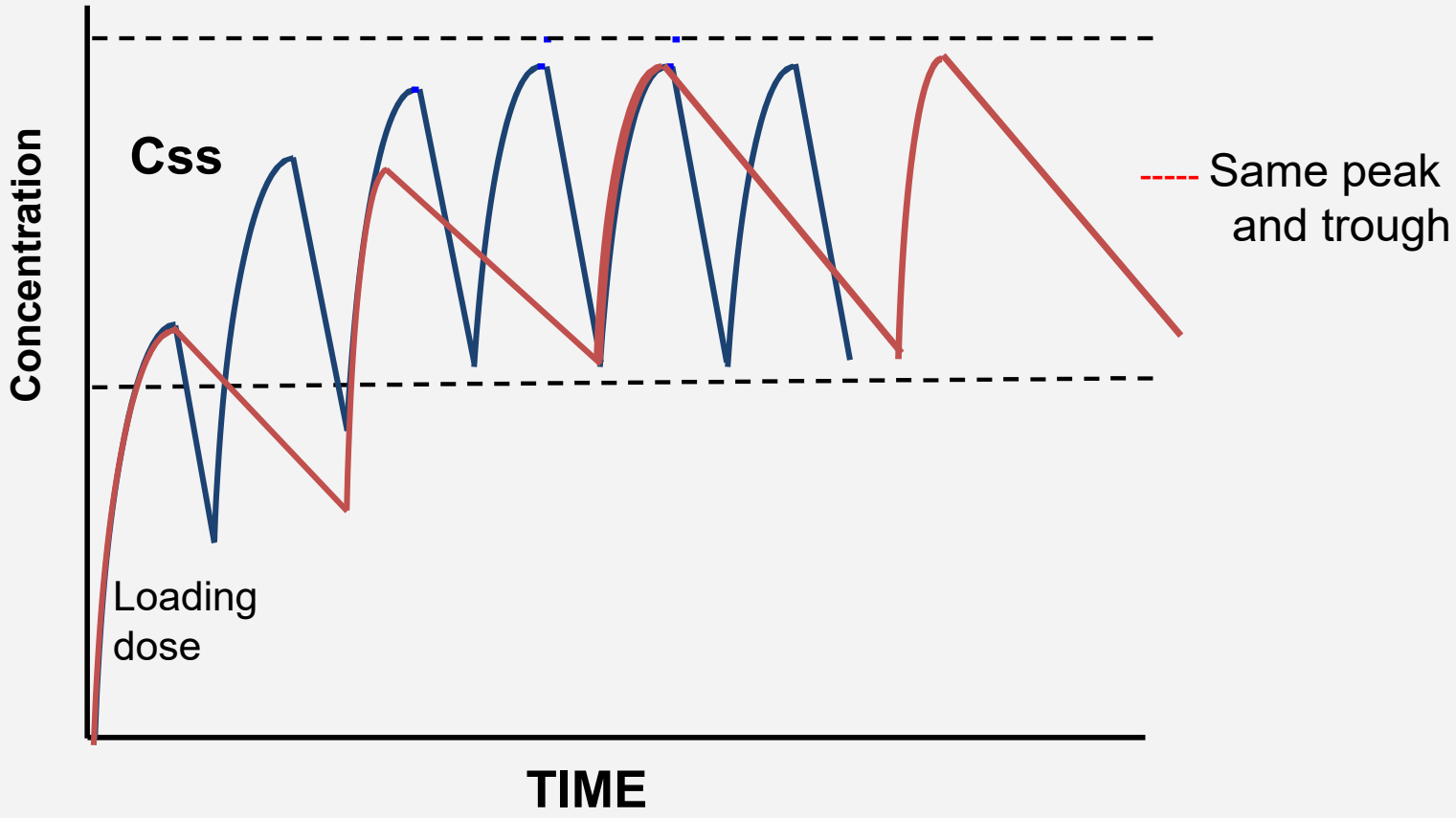
# Concentration Versus Time Profile with Normal and Reduced Kidney Function

***Same dose with extended dosing interval***




**Drug administered IV over 30 minutes**

***Assume the $V_D$ is the same**

**Blue: Normal kidney function**

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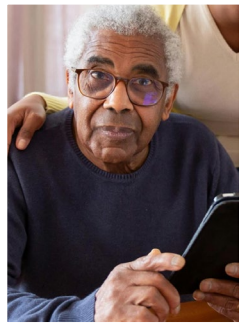
***Dashed lines represent the upper and lower drug level of the therapeutic range.***

# Case Study



| Patient |
| --- |
| RT is a 72-year-old, 89 kg male (Ht 6'2") who resides at home with his wife who is disabled<br><br>Allergies: NKDA |

| Labs/Vitals | Today | 6 mos ago |
| --- | --- | --- |
| A1c (%) | | 6.5 |
| K (mEq/L) | 4.9 | 4.5 |
| SCr (mg/dL) | 2.4 | 2.4 |
| eGFR (mL/min/1.73 $m^2$) | 28 | 28 |
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| UACR (mg/g) | 340 | 420 |
| Blood Pressure | 134/74 | 142/82 |

| PMH | |
| --- | --- |
| DM2 with neuropathy | Bipolar disorder |
| Atrial fibrillation | Seizure disorder |
| Chronic Kidney Disease Stage 3b | Osteoarthritis |

| Medications |
| --- |
| Acetaminophen 500 – 1000 mg PO PRN arthritis |
| Apixaban 5 mg PO BID |
| Atorvastatin 40 mg PO daily |
| Dapagliflozin 10 mg PO daily |
| Gabapentin 600 mg PO TID |
| Levetiracetam 1000 mg PO BID |
| Lisinopril 40 mg PO daily |
| Lithium 600 mg PO TID |
| Metformin 1000 mg PO BID |

# Question 3. Which drugs require a dose reduction in this patient? (Refer to a reference table by clicking on the “i” to the right of this slide)

| Medication | Yes | No |
|---|---|---|
| Acetaminophen | | |
| Apixaban | | |
| Atorvastatin | | |
| Dapagliflozin | | |
| Gabapentin | | |
| Levetiracetam | | |
| Lisinopril | | |
| Lithium | | |
| Metformin | | |

# Drug Characteristics and Dosing for Normal Kidney Function

| Drug | fe (%) of parent or active drug | $t_{1/2}$ (hrs) | Dose for normal kidney function |
|---|---|---|---|
| Acetaminophen | < 5 | ~2.5 | 325-650 every 406 hours PRN or 1 gram every 6 hours as needed |
| Apixaban | 27 | 12 | 5 mg BID (for afib)* |
| Atorvastatin | 0 | 14 | 40-80 mg daily (high intensity) |
| Dapagliflozin | < 2 | ~13 | 10 mg daily |
| Gabapentin | 100 | 5-7 | Max: 3600 mg day in 3 divided doses (for CrCl > 70 mL/min) for immediate release formulation |
| Levetiracetam | 66 | 6-8 | Max: 1500 mg BID for immediate release formulation |
| Lisinopril | 97 | 12 | 40 mg PO daily |
| Lithium | ~100 | 27 | Max: 900 – 1800 mg/day in 1-3 divided doses |
| Metformin | 90 | 4-9 | Usual maintenance: 850 – 1000 mg BID (max 2.55 g/day for immediate release formulation) |

**** Reduce to 2.5 mg bid if two of the following: Serum creatinine > 1.5 mg/dL, age ≥ 80 years and weight is ≤ 60 kg***

# Drug Characteristics and Dosing Recommendations

| Drug | fe (%) of parent or active drug | $t_{1/2}$ (hrs) | Dose for normal kidney function | Dose for reduced kidney function (based on the case presentation: $eGFR_{BSAadj}$ 35 mL/min) |
|---|---|---|---|---|
| **Acetaminophen** | < 5 | ~2.5 | 325-650 every 406 hours PRN or 1 gram every 6 hours as needed | |
| **Apixaban** | 27 | 12 | 5 mg BID (for afib)* | **If SCr < 1.5 mg/dL no change unless and weight criteria met*<br>If SCr ≥ 1.5 mg/dL change dose only if either age or weight criteria met*** |
| **Atorvastatin** | 0 | 14 | 40-80 mg daily (high intensity) | |
| **Dapagliflozin** | < 2 | ~13 | 10 mg daily | **Same as normal kidney function** |
| **Gabapentin** | 100 | 5-7 | Max: 3600 mg day in 3 divided doses (for CrCl > 70 mL/min) for immediate release formulation | **Max: 900 mg/day in 2-3 divided doses for CrCl 30-49 mL/min** |
| **Levetiracetam** | 66 | 6-8 | Max: 1500 mg BID for immediate release formulation | **Max: 750 mg every 12 hours** |
| **Lisinopril** | 97 | 12 | 40 mg PO daily | **Same as normal kidney function (monitor K and SCr, blood pressure)** |
| **Lithium** | ~100 | 27 | Max: 900 – 1800 mg/day in 1-3 divided doses | **Same as normal kidney function – start with lower dose when titrating and monitor lithium levels (range 0.8-1.2 mEq/L)** |
| **Metformin** | 90 | 4-9 | Usual maintenance: 850 – 1000 mg BID (max 2.55 g/day for immediate release formulation) | **Max: 500 mg BID** |

**** Reduce to 2.5 mg bid if two of the following: Serum creatinine > 1.5 mg/dL, age ≥ 80 years and weight is ≤ 60 kg***

# Balancing PK Information with Outcomes



## Examples

### Remdesivir

- fe of the vehicle used (SBECD) ~100%, associated with liver and kidney toxicity
- Initially not recommended if eGFR < 30 mL/min
- Manufacturer changed labelling to allow use with eGFR < 30 mL/min due to studies showing no increase in adverse effects in these individuals

### Apixaban

- fe 25%, adverse effect of bleeding is a serious concern
- No dose adjustment recommended for individuals with kidney failure treated for atrial fibrillation based on an 8-person single dose PK study however accumulation was reported in a multidose study.
- A propensity-matched cohort study of patients with kidney failure on hemodialysis found fewer thromboembolic events and major bleeding events with the full dose was used for atrial fibrillation

fe = fraction eliminated by the kidney

SBECD = sulfobutylether-beta-cyclodextrin

# Consider duration of drug therapy and acute situations…

Chronic therapy when drug accumulation may occur and persist over a prolonged period.

*vs*

Drug therapy needed for a shorter duration where accumulation less of a concern.

In the patient case:

- Apixaban
- Lithium
- Gabapentin
- Levetiracetam

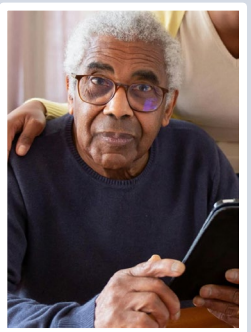
For example, during a hospitalization

- Cefepime given empirically
- Enoxaparin for DVT prophylaxis
- Morphine post surgery

Or for a short course by indication

- Remdesivir for COVID

# Case Study: Revisit

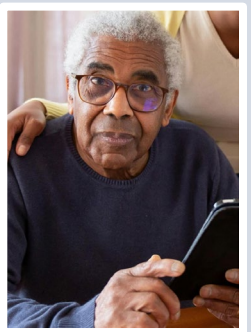


| Patient |
| --- |
| RT is admitted to the hospital after a fall and requires surgery for a fractured hip. He is started on enoxaparin for DVT prophylaxis. He also develops a fever and cough during the admission and is started on empiric antibiotics with vancomycin and cefepime. [weight 89 kg] |

| Labs/Vitals | Post surgery |
| --- | --- |
| Lithium (mEq/L) | 1.0 |
| K (mEq/L) | 4.4 |
| SCr (mg/dL) | 2.4 |
| eGFR (mL/min/1.73 $m^2$) | 28 |
| $eGFR_{BSAadj}$ (mL/min) | 35 |
| UACR (mg/g) | 340 |
| Blood Pressure | 122/65 |

| Medications |
| --- |
| Apixaban 5 mg BID [ON HOLD] |
| Atorvastatin 40 mg PO daily |
| **Cefepime 1 gram every 12 hours** |
| Dapagliflozin 10 mg PO daily |
| **Enoxaparin 40 mg SUBQ daily** |
| Gabapentin 300 mg PO BID |
| Levetiracetam 750 mg PO BID |
| Lisinopril 40 mg PO daily [ON HOLD] |
| Lithium 300 mg PO BID |
| Metformin 500 mg PO BID |
| **Morphine 1 mg every 4 hours PRN** |
| **Vancomycin 2000 mg x 1 dose** |

# Case Study: Revisit



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**Medications**

Apixaban 5 mg BID [ON HOLD]

Atorvastatin 40 mg PO daily

**Cefepime 1 gram every 12 hours (extended dosing interval)**

Dapagliflozin 10 mg PO daily

**Enoxaparin 40 mg SUBQ daily**

Gabapentin 300 mg PO BID

Levetiracetam 750 mg PO BID

Lisinopril 40 mg PO daily [ON HOLD]

Lithium 300 mg PO BID

Metformin 500 mg PO BID

**Morphine 1 mg every 4 hours PRN (avoid)**

**Vancomycin 2000 mg x 1 dose (extend dosing interval)**

# Patient Voice: How do we involve the patient? SHARE Approach

- Consider patient perspective – what do they care about?
  - Treating the condition
  - Avoiding adverse effects
  - Minimizing pill burden
  - Ease of regimen
  - Access/cost
- Share Approach
  - **S**eek individual's participation
  - **H**elp the patient explore and compare treatment options
  - **A**ssess the patient's values and preferences
  - **R**each a decision with the patient
  - **E**valuate the patient's decision

# Summary: What did we emphasize?

The PK processes of ADME are altered in individuals with CKD

Clinicians need to understand how these changes may affect drug concentrations which translates to risk of adverse events.

Altering the drug regimen for agents eliminated by the kidney is necessary to promote safe use of these agents.

The patient should be part of the decision process and understand the rationale for medication selection and the specific regimen as well as the potential safely implications.