FirstHope Notes | Pharm D Year - 5

Therapeutic Drug monitoring

Introduction to Therapeutic Drug Monitoring (TDM)

Definition:

- Therapeutic Drug Monitoring (TDM) refers to the clinical practice of measuring specific drug concentrations in a patient's biological fluids (typically plasma or serum) at designated intervals to ensure optimal therapeutic effect while minimizing toxicity.

Purpose and Key Objectives of TDM

TDM aims to:

1. **Individualize Therapy:** Tailor drug doses based on patient-specific pharmacokinetics and therapeutic response.
2. **Improve Efficacy:** Maintain drug levels within the therapeutic range for optimal effect.
3. **Minimize Toxicity:** Avoid adverse reactions by preventing concentrations above toxic thresholds.
4. **Assess Compliance:** Detect under- or over-dosing and monitor patient adherence.
5. **Support Clinical Decisions:** Aid in managing complex conditions involving organ dysfunction, drug interactions, or altered pharmacokinetics (e.g., in neonates, elderly, renal/hepatic impairment).

Key Features:

1. Primarily used for drugs with narrow therapeutic index (e.g., digoxin, phenytoin, lithium).
2. Requires understanding of pharmacokinetics (PK) and pharmacodynamics (PD).
3. Involves blood sampling at specific times (e.g., peak, trough, or steady-state levels).
4. Emphasizes individual variability rather than generalized dosing.

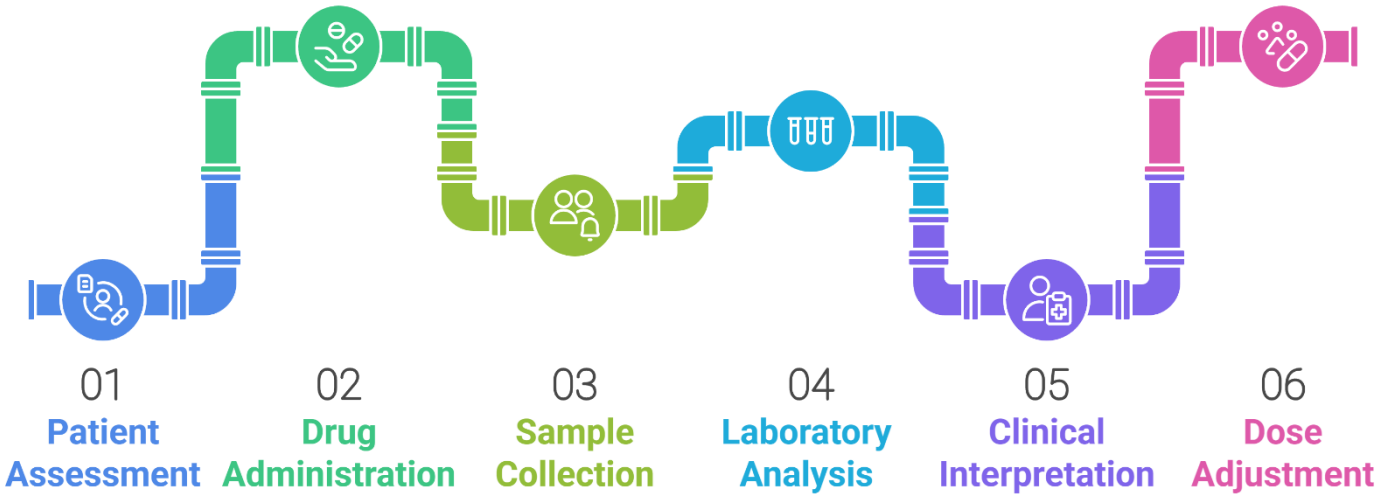
Ideal Drug Characteristics for TDM

- Drugs suitable for TDM typically exhibit:
    - A narrow therapeutic window.
    - High interindividual variability in drug metabolism or clearance.
    - Poor correlation between dose and clinical effect.
    - A well-established plasma concentration-effect relationship.
    - A defined therapeutic range.

Examples of Drugs Requiring TDM:

- **Antiepileptics**: Phenytoin, Valproic acid, Carbamazepine.
- **Cardiac drugs**: Digoxin, Procainamide.
- **Immunosuppressants**: Cyclosporine, Tacrolimus.
- **Psychiatric drugs**: Lithium, Clozapine.
- **Antibiotics**: Aminoglycosides (e.g., Gentamicin), Vancomycin.

Core Components of the TDM Process



1. Patient Assessment

- Review diagnosis, comorbidities, renal/hepatic function, and concurrent medications.

2. Drug Administration

- Document the prescribed dose, route, and frequency.

3. Sample Collection

- Timing is critical:
  - **Trough Level** – Just before the next dose; most commonly used.
  - **Peak Level** – Shortly after administration; useful for certain drugs like aminoglycosides.
  - **Steady State** – Typically measured after 4–5 half-lives.

4. Laboratory Analysis

- Performed using **immunoassays**, **high-performance liquid chromatography (HPLC)**, or **mass spectrometry**.

5. Clinical Interpretation

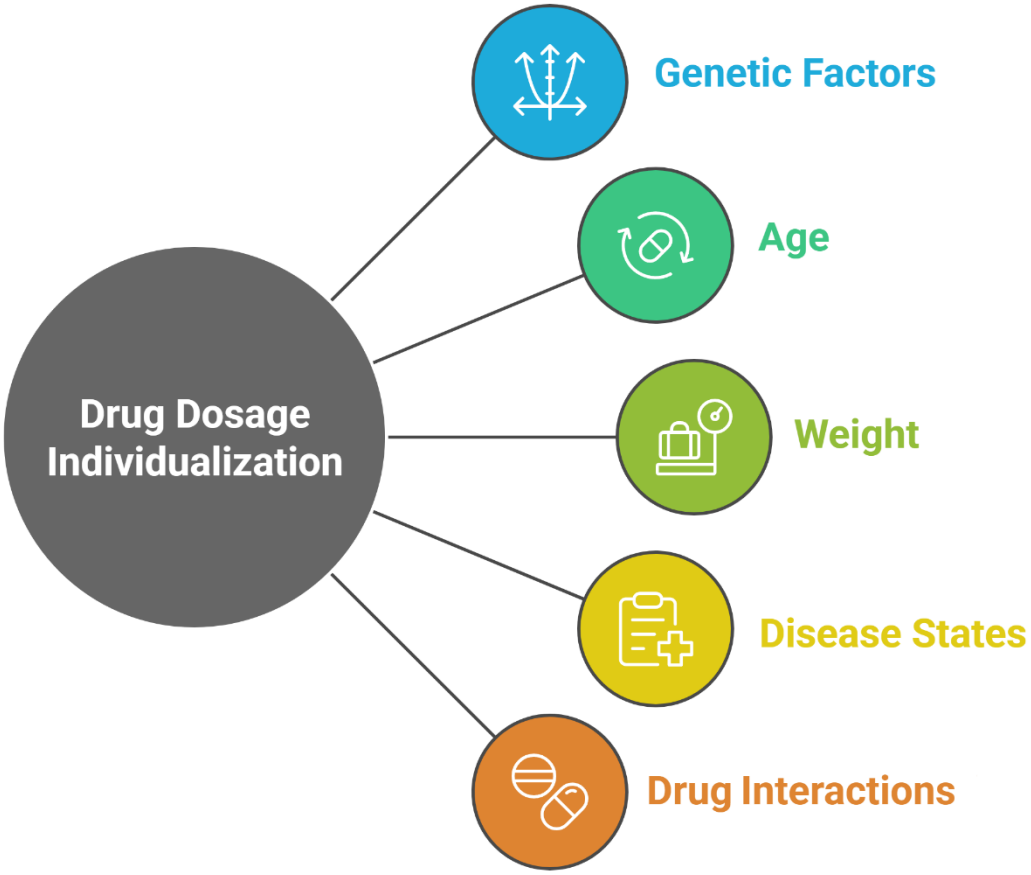
- Compare drug levels with therapeutic range while considering patient-specific factors and clinical response.

6. Dose Adjustment

- Modify dosing regimen based on interpretation and desired therapeutic outcome.

Individualization of Drug Dosage Regimen

- Therapeutic drug dosing must be customized for each patient based on a wide array of physiological, pathological, and external factors.
- Individual variability affects pharmacokinetics (PK) and pharmacodynamics (PD), making personalized dosing crucial to ensure efficacy and safety.



A. Genetic Variability (Pharmacogenetics / Pharmacogenomics)

- Genetic differences among individuals can significantly influence drug response.
- Pharmacogenetics is the study of how genetic variation affects an individual's response to drugs.

Key aspects include:

1. Drug Metabolizing Enzymes

- **Cytochrome P450 (CYP450)** enzymes metabolize over 70% of drugs.
- **Genetic polymorphisms** in these enzymes lead to different metabolizer phenotypes:
  - **Poor Metabolizers (PM)**: Minimal or no enzyme activity.
  - **Intermediate Metabolizers (IM)**: Reduced activity.
  - **Extensive Metabolizers (EM)**: Normal activity.
  - **Ultra-rapid Metabolizers (UM)**: Increased activity.
- **Example**:

- CYP2D6 polymorphism affects codeine metabolism.
  - PMs may get no analgesic effect.
  - UMs risk opioid toxicity due to rapid conversion to morphine.

2. Drug Transporters

- P-glycoprotein (ABCB1) polymorphisms affect drug absorption and distribution (e.g., digoxin, antidepressants).

3. Receptors and Targets

- Genetic variations in receptors (e.g., VKORC1 for warfarin) influence drug sensitivity and resistance.

Clinical Implications

- Genetic testing (e.g., TPMT genotyping for azathioprine) may be necessary.
- Pharmacogenomic profiling is used to personalize drug selection and dosing.

B. Age-Related Variability

Age significantly affects the pharmacokinetics and pharmacodynamics of drugs, necessitating dosage adjustments across the lifespan.

1. Neonates and Infants

- **Immature liver enzymes** → slower metabolism.
- **Reduced renal function** → delayed drug excretion.
- **Higher body water content** → affects distribution of hydrophilic drugs.
- **Lower plasma proteins** → increased free drug levels.

2. Elderly

- **Decline in renal function**, often underestimated by serum creatinine.
- **Slower hepatic metabolism**, especially phase I reactions.
- **Altered body composition** (↑ fat, ↓ water and lean mass).
- **Polypharmacy** increases risk of drug interactions.

Clinical Implications

- Pediatric and geriatric dosing often requires adjustment based on weight, body surface area (BSA), and renal function.
- TDM is particularly useful in elderly to prevent toxicity due to impaired clearance.

C. Weight-Related Variability

Drug dosage is often based on **body weight (mg/kg)** or **body surface area (mg/m^2)**, especially in children and chemotherapy patients.

1. Obesity

- **Lipophilic drugs** (e.g., diazepam): Larger volume of distribution → may require dose adjustment.
- **Hydrophilic drugs**: Dosing should not rely solely on total body weight.

2. Underweight / Cachexia

- Reduced plasma protein binding.
- Altered metabolism due to muscle wasting and organ impairment.

Dose Calculation Methods

- Use of Ideal Body Weight (IBW), Adjusted Body Weight (ABW), and BSA, depending on the drug.

D. Disease-Related Variability

Pathological states can drastically alter drug pharmacokinetics and dynamics.

1. Liver Disease

- Impaired **drug metabolism** (especially Phase I).
- **Reduced albumin** → higher free drug concentration.
- Drugs like **benzodiazepines, opioids, warfarin** often need dose reduction.

2. Kidney Disease

- Decreased **renal clearance** → accumulation of drug/metabolites.
- Drugs such as **aminoglycosides, lithium, digoxin** require close **TDM**.
- Use **Creatinine Clearance (CrCl)** or **eGFR** for dosing.

3. Cardiac Failure

- **Reduced hepatic/renal perfusion** impairs clearance.
- **Edema** alters drug distribution.

4. Gastrointestinal Disorders

- Conditions causing malabsorption reduce drug bioavailability.
- Vomiting/diarrhea interfere with oral drug effectiveness.

E. Drug Interactions (PK and PD)

Concomitant use of multiple drugs (polypharmacy) can lead to pharmacokinetic and pharmacodynamic interactions, affecting drug levels or response.

1. Pharmacokinetic Interactions

- **Absorption**: Antacids decrease bioavailability of drugs like tetracyclines.
- **Metabolism**:
  - **Inhibitors** (e.g., erythromycin, ketoconazole) ↑ drug levels.

- **Inducers** (e.g., rifampin, carbamazepine) ↓ drug levels.

2. Pharmacodynamic Interactions

- **Synergistic Toxicity**: NSAIDs + aminoglycosides ↑ nephrotoxicity.
- **Antagonistic Effects**: Warfarin + vitamin K-rich foods ↓ anticoagulant effect.

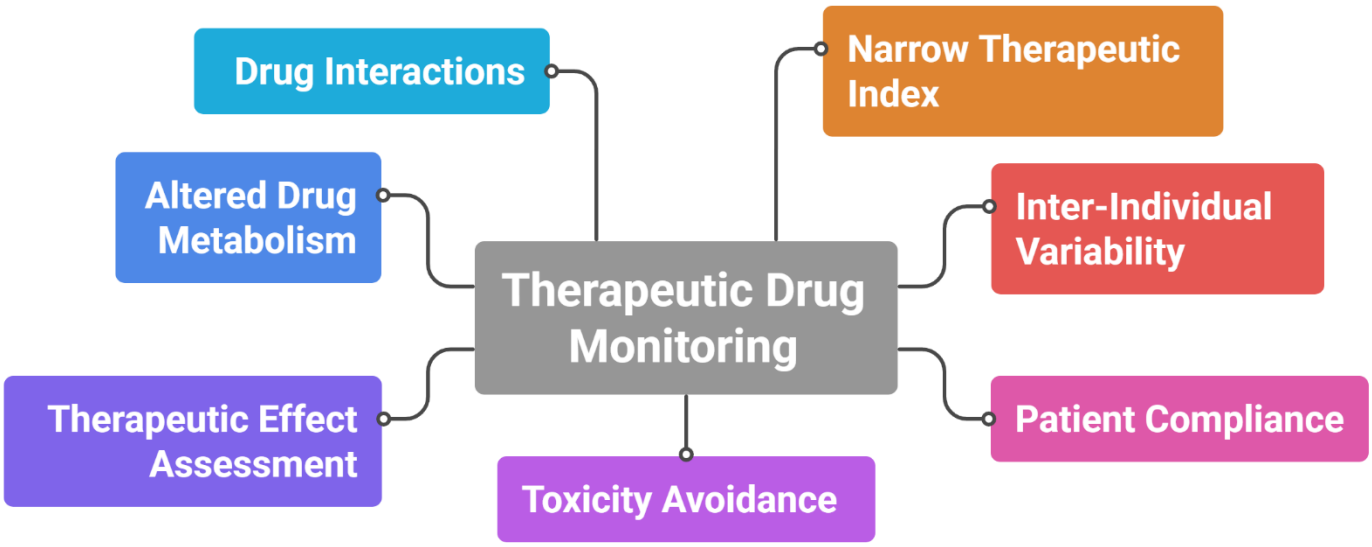
Clinical Strategy

- TDM is essential when initiating or discontinuing interacting drugs.
- Dosages should be re-evaluated at new steady-state concentrations.

Indications for Therapeutic Drug Monitoring (TDM)

- TDM is not performed for all medications.
- Its use is justified only under specific clinical circumstances where monitoring enhances therapeutic outcomes.
- The decision to conduct TDM is based on the pharmacological properties of the drug and patient-related factors.

Major Indications for TDM



A. Drugs with a Narrow Therapeutic Index (NTI):

- These are drugs where the difference between therapeutic and toxic concentrations is small.
- Slight deviations from the therapeutic range may lead to either treatment failure or toxicity.
- **Examples**: Digoxin, phenytoin, lithium, theophylline, cyclosporine.

B. Significant Inter-Individual Variability:

- Drugs that exhibit high variability in pharmacokinetics (absorption, metabolism, distribution, or elimination) between individuals.
- TDM helps determine the correct dose for each patient.

C. Monitoring Patient Compliance:

- TDM can reveal whether a patient is taking the drug as prescribed.
- Especially important in chronic conditions like epilepsy or psychiatric illnesses.

D. To Avoid or Identify Toxicity:

- When clinical symptoms suggest drug toxicity, TDM can confirm elevated serum drug levels.
- Useful for early detection before irreversible damage occurs.

E. To Assess Lack of Therapeutic Effect:

- If a patient is not responding to treatment, TDM can help determine if it is due to subtherapeutic levels or drug resistance.

F. Altered Drug Metabolism or Clearance:

- In patients with **renal**, **hepatic**, or **cardiac dysfunction**, drug clearance may be impaired.
- TDM helps prevent accumulation and toxicity.

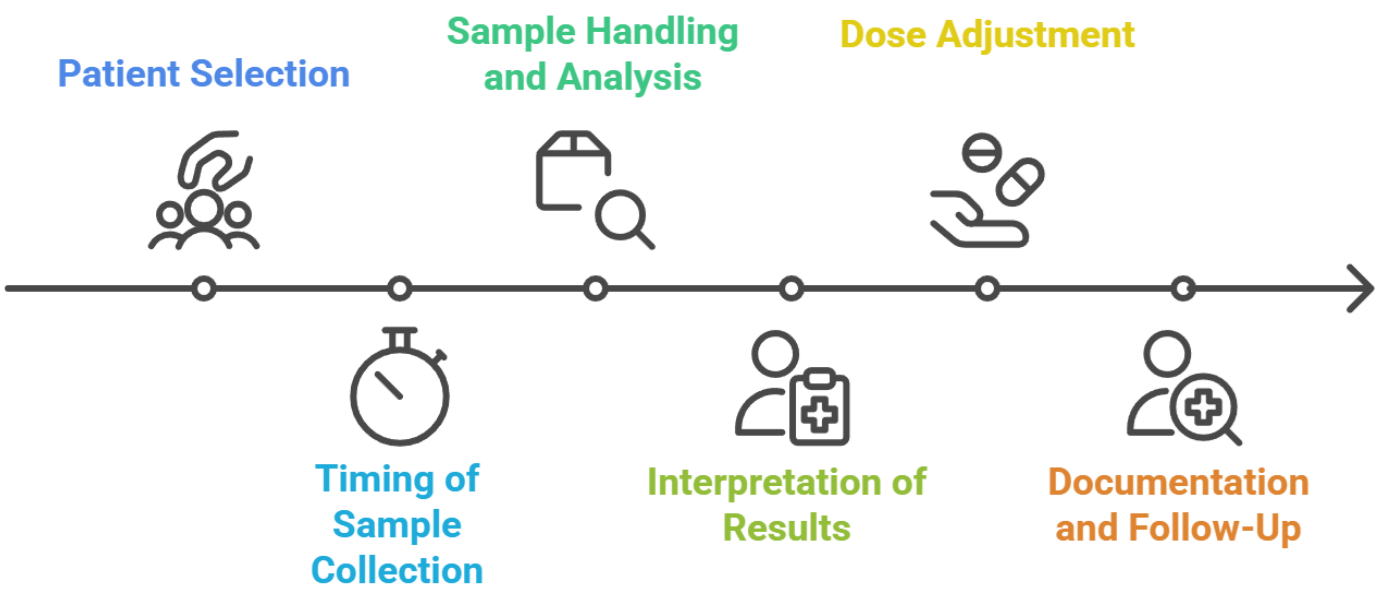
G. Drug Interactions:

- Co-administration of other drugs may affect metabolism or elimination.
- TDM helps adjust the dose appropriately.

Protocol for TDM

- TDM is not just about measuring drug concentrations.
- It is a systematic clinical process involving the collaboration of physicians, pharmacists, nurses, and laboratory staff. The steps ensure that the test results are accurate, relevant, and interpretable.

Step-by-Step Protocol for TDM



1. Patient Selection:

- TDM is only appropriate for specific drugs and clinical situations.
- Selection should be based on:
  - Drug characteristics (e.g., narrow therapeutic index)
  - Patient condition (e.g., renal or hepatic dysfunction)
  - Clinical goal (e.g., optimize dose, assess compliance)

2. Timing of Sample Collection:

- **Timing is critical** for accurate interpretation.
- Based on the pharmacokinetics of the drug (half-life, steady-state).
- Common timing strategies:
  - **Trough level**: Just before the next dose. Best for most drugs.
  - **Peak level**: Short time after dose administration. Important for drugs like aminoglycosides.
  - **Steady-state levels**: Usually achieved after 4–5 half-lives of regular dosing.
- *Example*:
  - **For digoxin:** Blood should be drawn at least 6–8 hours after the last dose.
  - **For aminoglycosides:** Both peak and trough levels may be needed.

3. Sample Handling and Analysis:

- Proper handling is essential to avoid degradation or contamination.
- Use appropriate anticoagulants or preservatives.
- Transport to laboratory under recommended conditions.
- Analytical methods:
  - **Immunoassays** (e.g., ELISA, EMIT) – fast, but may lack specificity.
  - **Chromatographic methods** (e.g., HPLC, LC-MS) – more accurate and specific.

4. Interpretation of Results:

- Interpretation must be individualized.
- Consider:
  - Time of sample collection relative to dosing.
  - Route of administration.
  - Patient's clinical status.
  - Co-administered drugs.
  - Organ function (renal, hepatic).
- Results are interpreted against the therapeutic range or target concentration, considering:
- Is the drug level therapeutic, subtherapeutic, or toxic?
- Are symptoms consistent with the drug concentration?

5. Dose Adjustment:

- Based on the drug level and clinical response, dosing may need to be increased, decreased, or continued as is.

- Adjustments should also account for changes in renal or hepatic function, or drug interactions.

6. Documentation and Follow-Up:

- Every step should be recorded: time of last dose, time of sample collection, method of measurement, results, and dose changes.
- Ongoing monitoring may be required depending on:
  - Clinical response
  - Changes in patient condition
  - Introduction of new medications

Pharmacokinetic/Pharmacodynamic Correlation in Drug Therapy

Overview

- The effectiveness of TDM depends heavily on understanding how pharmacokinetics (PK) and pharmacodynamics (PD) are interlinked.

Pharmacokinetics (PK)

- This refers to what the body does to the drug, encompassing:
  - **Absorption** – Entry of drug into circulation.
  - **Distribution** – Dispersal of drug to tissues.
  - **Metabolism** – Conversion to active/inactive forms.
  - **Excretion** – Removal from the body.
- These parameters determine plasma drug concentrations at various time points.

Pharmacodynamics (PD)

- This refers to what the drug does to the body, describing:
  - **Mechanism of action**
  - **Dose-response relationship**
  - **Therapeutic effects**
  - **Adverse effects**
- PD defines the magnitude and duration of the drug's effect at a given concentration.

Purpose of PK/PD Correlation in TDM

- To ensure the drug concentration at the site of action is sufficient for the desired effect.
- To avoid toxicity due to excessively high concentrations.
- To adjust the dose based on individual response and drug levels.
- To develop optimal dosage regimens for complex cases.

Key PK/PD Parameters Used in TDM

Parameter	Definition	Clinical Significance
Cmin (Trough Level)	Lowest concentration before next dose	Ensures therapeutic level throughout dosing interval (important for antibiotics, anticonvulsants)
Cmax (Peak Level)	Highest concentration after dose	Key for concentration-dependent drugs (e.g., aminoglycosides)

AUC (Area Under the Curve)	Total drug exposure over time	Used in oncology and antibiotics (e.g., vancomycin AUC/MIC > 400)
t½ (Half-life)	Time for plasma concentration to reduce by half	Determines dosing interval and steady-state time
Therapeutic Range	Concentration between MEC and MTC	Defines effective and safe concentration limits

Types of PK/PD Models

Model Type	Description	Example
Direct Link Model	Effect correlates directly with plasma concentration	Digoxin
Delayed Response Model	Effect lags behind concentration	Warfarin
Indirect Response Model	Drug alters mediator synthesis/removal	Corticosteroids
Hysteresis Model	Time delay between concentration and effect (looped curve)	CNS drugs (e.g., antipsychotics)

Types of PK/PD Relationships

A. Concentration-Effect Relationship:

- **Emax Model**: Describes maximum effect at a plateau concentration.

$$E = \frac{E_{max} \cdot C}{EC_{50} + C}$$

- **where:**
  - E: observed effect
  - E_{max}: maximal effect
  - C: drug concentration
  - EC_{50}: concentration at 50% of maximal effect

B. Time-Dependent vs. Concentration-Dependent Killing (for antibiotics):

Killing Type	Key Factor	Example Drugs
Time-Dependent	Time drug remains above MIC	β-lactams, Vancomycin
Concentration-Dependent	Peak/MIC ratio	Aminoglycosides, Fluoroquinolones

C. Therapeutic Window Concept:

- The range between minimum effective concentration (MEC) and minimum toxic concentration (MTC).
- TDM aims to maintain levels within this window.

PK/PD Indices for Antibiotics

Index	Application	Example Drugs
Time > MIC	Time-dependent killing	Beta-lactams, Vancomycin
Cmax/MIC	Concentration-dependent killing	Aminoglycosides
AUC/MIC	Total exposure vs. MIC	Vancomycin, Fluoroquinolones

Clinical Application of PK/PD in TDM

- By integrating PK and PD data, clinicians can:
  - Predict therapeutic response and toxicity.
  - Determine optimal sampling times and dosing schedules.
  - Decide monitoring frequency based on half-life and clinical condition.

Challenges in PK/PD Correlation

- Plasma concentration may not reflect the actual concentration at the site of action.
- Inter-patient variability in metabolism and response.
- Delayed PD effect despite therapeutic PK levels (e.g., warfarin, antidepressants).

Example Applications:

Drug	PK/PD Target	Use in TDM
Vancomycin	AUC/MIC > 400	Adjust dose based on trough level or AUC estimation
Aminoglycosides	Cmax/MIC > 10	Monitor both peak and trough for efficacy and toxicity
Phenytoin	Total concentration within 10–20 µg/mL	Non-linear kinetics; adjust dose carefully
Digoxin	Trough 0.5–2 ng/mL	Risk of toxicity; monitor in elderly and renal dysfunction

Various TDM of Drugs in Specific Disease Conditions

Cardiovascular Diseases: TDM of drugs used

Overview

- In cardiovascular therapy, TDM ensures therapeutic efficacy while preventing toxicity such as arrhythmias and bleeding.
- Variability in drug response due to age, renal function, hepatic impairment, or drug–drug interactions makes monitoring essential.

Key Drugs and Their Monitoring

1. Digoxin

- **Indication:** Congestive heart failure, atrial fibrillation
- **Therapeutic Range:** 0.8–2.0 ng/mL (some guidelines prefer < 1.2 ng/mL to minimize mortality risk)
- **Pharmacokinetic Considerations:**
  - Long half-life (36–48 hours)
  - Primarily renal elimination → dose reduction in renal impairment
  - Interactions: Verapamil, amiodarone, and quinidine increase digoxin levels
- **Toxicity:** Arrhythmias, nausea, visual disturbances ("yellow vision")
- **Monitoring:** Trough levels 6–8 hours post-dose

2. Antiarrhythmics

- **Procainamide:**
  - Therapeutic Range: 4–10 µg/mL
  - Combined with N-acetylprocainamide (NAPA): 10–30 µg/mL
  - Monitoring prevents proarrhythmic toxicity
- **Lidocaine:**
  - **Therapeutic Range:** 1.5–5 µg/mL
  - **Toxicity:** CNS effects such as dizziness, confusion, or seizures

3. Warfarin

- **Monitoring Parameter:** INR (not serum levels)
- **Target INR:**
  - 2–3 → most indications (e.g., atrial fibrillation, DVT)
  - 2.5–3.5 → mechanical heart valves
- **Factors Affecting INR:**

- Genetic polymorphisms in VKORC1 and CYP2C9
- Drug interactions (antibiotics, antifungals, NSAIDs)
- Diet rich in vitamin K

Summary Table

Drug	Use	Therapeutic Range	Key Notes
Digoxin	CHF, Atrial fibrillation	0.8–2.0 ng/mL	Renal elimination; toxicity: arrhythmia, visual changes; monitor 6–8h post-dose
Procainamide	Arrhythmias	4–10 µg/mL (w/ NAPA: 10–30)	Monitor both drug + metabolite to prevent proarrhythmia
Lidocaine	Ventricular arrhythmias	1.5–5 µg/mL	CNS toxicity; short half-life
Warfarin	Anticoagulation	INR 2–3 (2.5–3.5 if valve)	Genetic & drug interaction variability; Vitamin K intake affects INR

Seizure Disorders (Epilepsy): TDM of drugs used

Overview

- Antiepileptic drugs (AEDs) have variable pharmacokinetics, drug interactions, and narrow therapeutic ranges.
- TDM ensures consistent serum levels, preventing seizures and minimizing CNS toxicity.

Key Drugs and Their Monitoring

1. Phenytoin

- **Therapeutic Range:** 10–20 µg/mL (free: 1–2 µg/mL)
- **Pharmacokinetics:** Non-linear (zero-order at high concentrations)
- **Monitoring:** Both total and free levels, especially in hypoalbuminemic patients
- **Toxicity:** Nystagmus, ataxia, gingival hyperplasia, cognitive dysfunction
- **Interactions:** Strong CYP enzyme inducer (e.g., enhances metabolism of other drugs)

2. Valproic Acid

- **Therapeutic Range:** 50–100 µg/mL (up to 125 µg/mL in mania)
- **Toxicity:** Hepatotoxicity, hyperammonemia, thrombocytopenia
- **PK Characteristics:** High protein binding, saturable binding at higher doses

3. Carbamazepine

- **Therapeutic Range:** 4–12 µg/mL
- **Special Feature: Autoinduction** – increases its own metabolism over time
- **Toxicity:** Hyponatremia, rash (Stevens–Johnson syndrome), blood dyscrasias

4. Phenobarbital

- **Therapeutic Range:** 15–40 µg/mL
- **Half-Life:** 80–120 hours
- **Uses:** Neonatal seizures, refractory epilepsy

Summary Table

Drug	Use	Therapeutic Range	Key Notes
Phenytoin	Epilepsy	10–20 µg/mL (free: 1–2)	Non-linear PK; monitor free drug if low albumin; CYP inducer
Valproic Acid	Epilepsy, Bipolar	50–100 µg/mL (up to 125)	Hepatotoxicity, protein binding saturation
Carbamazepine	Epilepsy	4–12 µg/mL	Autoinduction; monitor for SJS, hyponatremia
Phenobarbital	Neonatal/refractory	15–40 µg/mL	Very long half-life (80–120 hrs)

Clinical Role of TDM

- Maintain therapeutic plasma levels for seizure control
- Guide dose adjustments during growth, pregnancy, or hepatic dysfunction
- Detect non-adherence
- Identify toxicity or drug interactions in polytherapy

Psychiatric Conditions: TDM of drugs used

Overview

- Psychiatric drugs often require TDM due to variability in metabolism, adherence issues, and narrow therapeutic windows.
- Monitoring helps balance efficacy with avoidance of toxicity.

Key Drugs and Their Monitoring

1. Lithium

- **Indication:** Bipolar disorder (acute mania and maintenance therapy)

- **Therapeutic Range:** 0.6–1.2 mEq/L
- **Monitoring:** Trough level (12 hours post-dose)
- **Elimination:** Renal → adjust in renal impairment
- **Interactions:** Diuretics, NSAIDs, and ACE inhibitors increase toxicity risk
- **Toxicity:** Tremors, nephrotoxicity, hypothyroidism, seizures

2. Clozapine

- **Indication:** Treatment-resistant schizophrenia
- **Therapeutic Range:** 350–600 ng/mL
- **Toxicity:** Agranulocytosis, seizures, myocarditis
- **Monitoring Parameters:** Plasma concentration + absolute neutrophil count (ANC)
- **Metabolism:** CYP1A2; affected by smoking, caffeine intake

3. Tricyclic Antidepressants (TCAs)

- **Examples:** Nortriptyline, Amitriptyline
- **Therapeutic Range (Nortriptyline):** 50–150 ng/mL
- **Toxicity:** Cardiotoxicity, strong anticholinergic effects
- **Significance:** TDM minimizes overdose risk and enhances therapeutic response

Summary Table

Drug	Use	Therapeutic Range	Key Notes
Lithium	Bipolar disorder	0.6–1.2 mEq/L	Renal excretion; monitor 12h post-dose; toxicity w/ NSAIDs, diuretics
Clozapine	Resistant schizophrenia	350–600 ng/mL	Monitor ANC; risk of agranulocytosis; metabolism via CYP1A2
TCAs (e.g., Nortriptyline)	Depression	50–150 ng/mL	Anticholinergic + cardiac toxicity; used in overdose risk assessment

Organ Transplantation: TDM of drugs used

Overview

- TDM of immunosuppressive agents is crucial to prevent graft rejection and minimize drug-induced toxicity.
- High interindividual variability arises from differences in metabolism, absorption, and drug interactions.

Key Drugs and Their Monitoring

1. Cyclosporine

- **Therapeutic Range:**
  - **Initial Phase:** 150–300 ng/mL
  - **Maintenance:** 100–200 ng/mL
- **Monitoring Methods:** Trough (C_0) or 2 hours post-dose (C_2)
- **Toxicity:** Nephrotoxicity, hypertension, hirsutism
- **Metabolism:** CYP3A4 substrate → interactions with azoles, macrolides, grapefruit juice

2. Tacrolimus

- **Therapeutic Range:** 5–15 ng/mL (depends on organ type and post-transplant duration)
- **Toxicity:** Nephrotoxicity, neurotoxicity, hyperglycemia
- **Monitoring:** Trough levels
- **Metabolism:** CYP3A4 → numerous interactions

3. Sirolimus (Rapamycin)

- **Therapeutic Range:** 5–15 ng/mL
- **Half-Life:** ~60 hours → delayed steady-state achievement
- **Toxicity:** Hyperlipidemia, thrombocytopenia, impaired wound healing
- **Monitoring:** Regular due to variable absorption and metabolic interactions

4. Mycophenolate

- **Use:** Often combined with other immunosuppressants
- **TDM:** Less commonly performed; useful in cases of toxicity or poor response

Summary Table

Drug	Use	Therapeutic Range	Key Notes
Cyclosporine	Organ transplant	100–300 ng/mL	C_0 or C_2 monitoring; CYP3A4 interactions; nephrotoxic
Tacrolimus	Organ transplant	5–15 ng/mL	Trough levels; nephro/neurotoxicity; CYP3A4 substrate
Sirolimus	Maintenance immunosuppression	5–15 ng/mL	Delayed steady state (t½ ~60h); monitor lipid, platelet effects
Mycophenolate	Adjunct immunosuppressant	Variable (TDM rare)	Consider TDM only in poor response or toxicity

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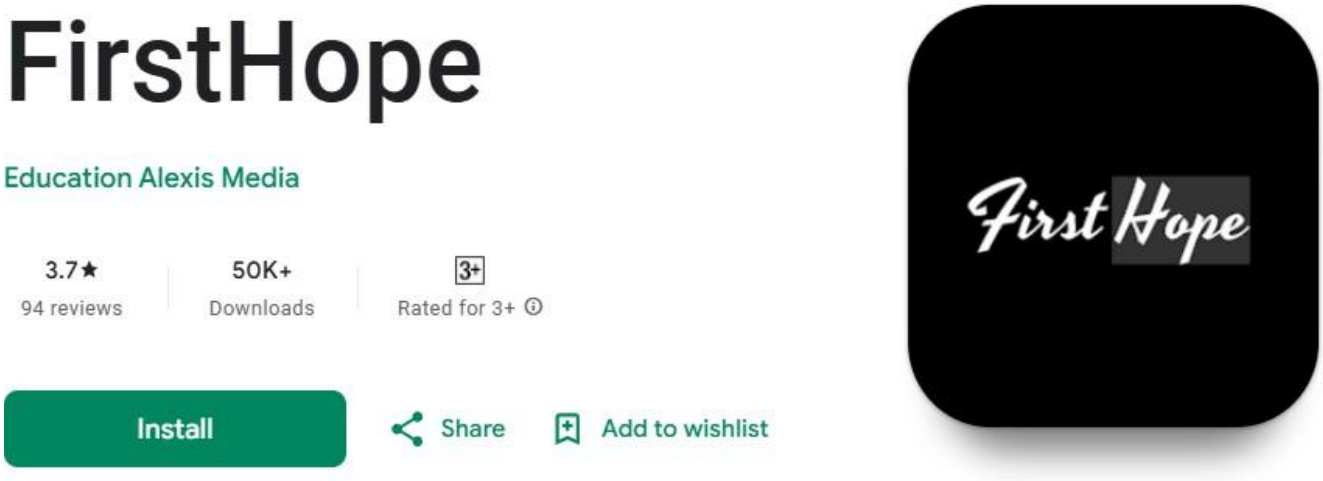

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