

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:

- Individualize Therapy:** Tailor drug doses based on patient-specific pharmacokinetics and therapeutic response.
- Improve Efficacy:** Maintain drug levels within the therapeutic range for optimal effect.
- Minimize Toxicity:** Avoid adverse reactions by preventing concentrations above toxic thresholds.
- Assess Compliance:** Detect under- or over-dosing and monitor patient adherence.
- 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:

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

Ideal Drug Characteristics for TDM

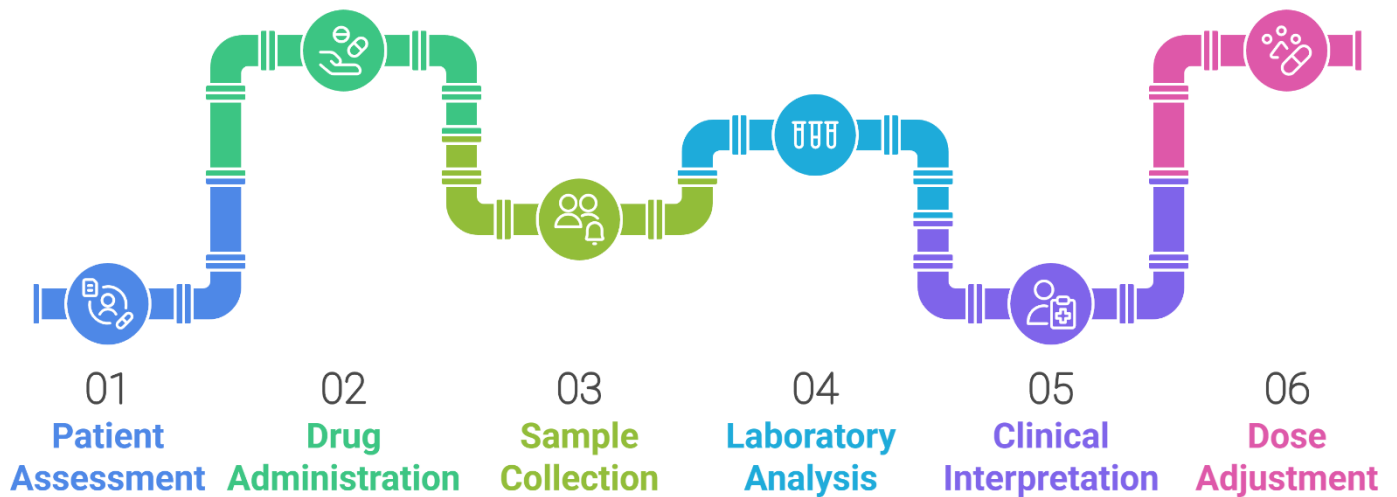
- Drugs suitable for TDM typically exhibit:
 - A narrow therapeutic window.
 - High interindividual variability in drug metabolism or clearance.
 - Poor correlation between dose and clinical effect.
 - A well-established plasma concentration-effect relationship.
 - A defined therapeutic range.

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

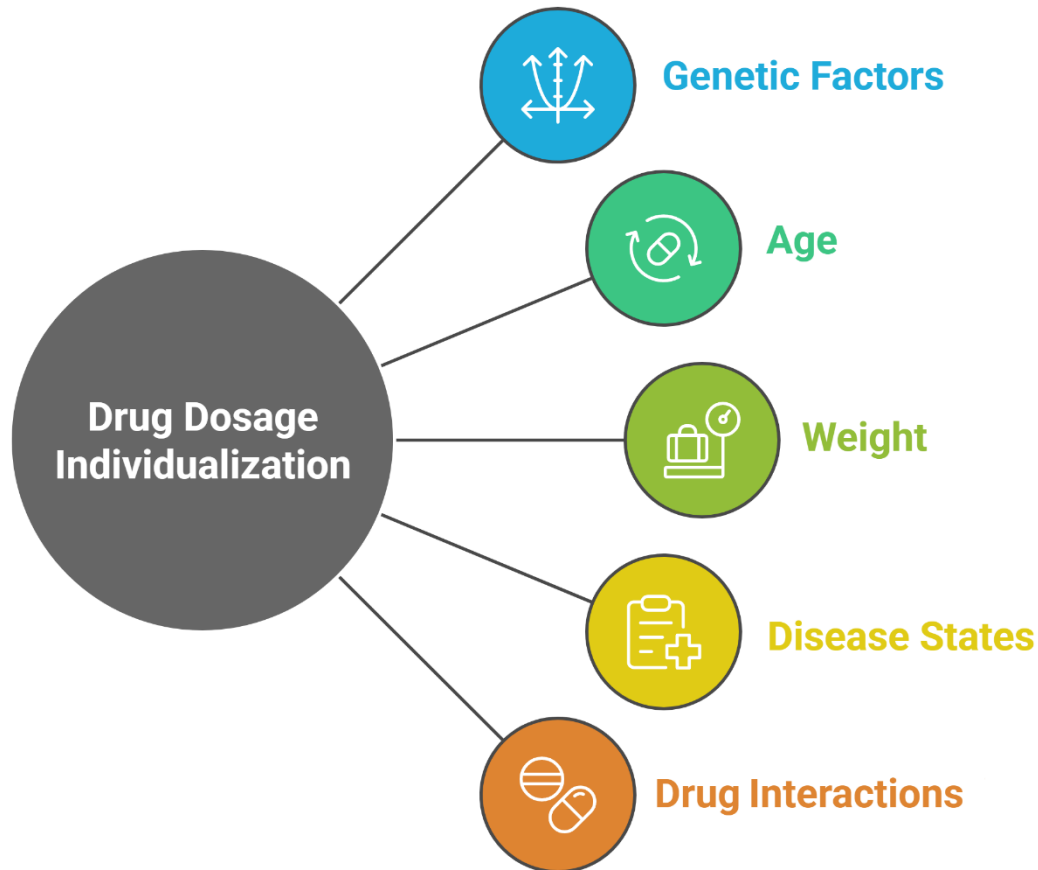
- Compare drug levels with therapeutic range while considering patient-specific factors and clinical response.

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/m²)**, 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.



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