CHAPTER 9

DRUG THERAPY OPTIMIZATION

Author

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Abstract

Drug therapy optimization represents the systematic process of maximizing therapeutic benefits while minimizing risks through personalized medication selection and management strategies. Dosing considerations incorporate pharmacokinetic principles, physiological variations, and disease-specific factors requiring individualized adjustment based on renal function, hepatic status, age, weight, and genetic factors affecting drug disposition. Drug interaction management addresses pharmacokinetic and pharmacodynamic mechanisms requiring systematic screening, clinical significance assessment, and mitigation strategies including dose adjustment, spacing administration, or alternative therapy selection. Adverse effect prevention and management employs risk factor identification, proactive monitoring, and intervention protocols balancing therapeutic benefits against potential harms through structured assessment tools and documentation systems. Special population adaptation addresses unique considerations for pediatric, geriatric, pregnant, and physiologically compromised patients requiring specific dosing algorithms, monitoring parameters, and safety precautions. Cost consideration strategies integrate economic factors with clinical decision-making through formulary management, therapeutic interchange, assistance program navigation, and value assessment methodologies. This comprehensive approach ensures patients receive medications optimally matched to their specific needs, characteristics, and circumstances.

Keywords: *Pharmacokinetic Optimization, Patient-Specific Dosing, Polypharmacy Management, Benefit-Risk Assessment, Therapeutic Individualization*

Learning Objectives

After completion of the chapter, the learners should be able to:

- Calculate and adjust medication dosages based on patient-specific factors including renal function, hepatic status, weight, age, and pharmacogenetic considerations.
- Identify clinically significant drug interactions and implement appropriate management strategies including dose adjustment, scheduling changes, or alternative therapy selection.
- Develop comprehensive plans for preventing, monitoring, and managing medication adverse effects through risk factor identification and systematic monitoring.
- Modify drug therapy approaches for special populations including pediatric, geriatric, pregnant, and physiologically compromised patients requiring specialized dosing and monitoring.
- Implement cost-effectiveness strategies including formulary management, therapeutic interchange, and assistance program utilization to optimize medication affordability.
- Integrate pharmacokinetic principles into patient-specific dosing regimens for narrow therapeutic index medications requiring individualized approaches.

DOSING CONSIDERATIONS

Weight-based dosing implements appropriate calculations based on actual, ideal, or adjusted body weight depending on medication characteristics, with lipophilic drugs (e.g., benzodiazepines, phenytoin) typically using actual weight while hydrophilic medications (e.g., aminoglycosides, many antimicrobials) may require adjusted calculations for obese patients. Age-related adjustments account for physiological changes across the lifespan, with pediatric dosing based on weight, body surface area, or age bands reflecting developmental pharmacokinetics, while geriatric dosing often requires reduction due to decreased renal function, altered body composition, and increased sensitivity to many medications. Organ function considerations adjust dosing based on elimination pathway impairment, with medications cleared renally requiring systematic modification based on creatinine clearance or eGFR, while hepatically metabolized drugs may require empiric dose reduction or monitoring based on liver function parameters.

Table 9.1: Patient-Specific Dosing Considerations

Dosing Factor	Assessment Parameters	Adjustment	Monitoring
Renal Function	Serum creatinine, eGFR (CKD-EPI, Cockcroft-Gault), urinary markers	Dose reduction, interval extension, alternative agent	Renal function trends, drug levels, efficacy/toxicity markers
Hepatic Function	Liver enzymes, Child-Pugh score, albumin, coagulation	Dose reduction, empiric adjustment, alternative agent	Liver function tests, drug levels, clinical toxicity signs
Age-Related Factors	Physiological age, organ function, frailty assessment	Start low-go slow approach, geriatric-specific guidelines	Enhanced adverse effect monitoring, functional assessments
Body Size/Composition	Actual vs. ideal body weight, BMI, body surface area, lean body mass	Weight-based calculations, capping doses, composition adjustments	Therapeutic response, concentration monitoring, effect assessment
Genetic Variations	Pharmacogenetic testing, ancestry considerations, response history	Genotype-guided dosing, alternative pathway drugs, dose adjustments	Enhanced monitoring for variant phenotypes, efficacy/toxicity assessment
Comorbid Conditions	Disease states affecting PK/PD, organ function impact, drug-disease interactions	Disease-specific adjustments, alternative agents, enhanced monitoring	Disease-specific parameters, drug response in comorbidity context
Pregnancy/Lactation	Trimester, physiological changes, placental transfer, breast milk excretion	Pregnancy-specific dosing, risk-benefit assessment, alternative agents	Maternal/fetal monitoring, postpartum adjustment, infant observation

Dosing Factor	Assessment Parameters	Adjustment	Monitoring
Pediatric Considerations	Age, weight, body surface area, developmental stage	Weight-based dosing, age-specific formulations, developmental adjustments	Growth parameters, developmental assessments, age-appropriate monitoring
Extracorporeal Therapy	Dialysis modality, CRRT settings, dialyzer characteristics, timing	Supplemental doses, timing relative to dialysis, alternative agents	Pre/post-dialysis levels, clinical response monitoring, residual function

Pharmacokinetic Principles

Loading dose calculation implements appropriate initial administrations establishing therapeutic concentrations rapidly for medications with long half-lives or delayed onset, with amount typically based on volume of distribution and target concentration independent of elimination function. Maintenance dose determination balances drug input with elimination based on clearance parameters, dosing interval, and desired steady-state concentrations, adjusting for individual patient factors affecting drug disposition. Dosing interval selection considers pharmacokinetic properties including half-life, therapeutic index, and concentration-effect relationships, with narrow therapeutic index drugs often requiring more frequent administration to minimize peak-trough fluctuations compared to medications with wider safety margins.

Specialized Dosing Approaches

Extended-interval dosing implements less frequent administration of larger doses based on concentration-dependent efficacy and post-antibiotic effect, particularly valuable for aminoglycosides (once-daily versus traditional three-times daily) reducing nephrotoxicity while maintaining effectiveness. Individualized pharmacokinetic dosing employs patient-specific parameters in formal pharmacokinetic models, using Bayesian approaches incorporating population parameters, individual drug levels, and patient characteristics to optimize therapy for narrow therapeutic index medications including vancomycin, aminoglycosides, and anticonvulsants. Continuous infusion strategies maintain consistent drug concentrations for medications where constant levels optimize effect (e.g., beta-lactam antibiotics, some anticoagulants), potentially improving efficacy while reducing toxicity compared to

intermittent administration.

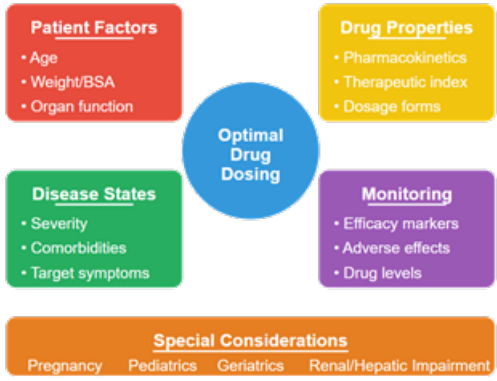

Figure 9.1: Dosing Considerations

Route of Administration Considerations

Bioavailability adjustment accounts for incomplete absorption of many oral medications compared to intravenous administration, with dose increases typically necessary when converting from parenteral to oral therapy for medications with poor bioavailability including many fluoroquinolones, antifungals, and immunosuppressants. First-pass metabolism considerations address extensive hepatic extraction reducing systemic availability of orally administered medications including morphine, propranolol, and many antipsychotics, potentially requiring higher oral doses or alternative routes when hepatic function changes. Alternative route selection evaluates options including subcutaneous, intramuscular, transdermal, sublingual, or rectal administration when conventional routes are unavailable or inappropriate, with each alternative requiring specific dose adjustments based on absorption characteristics and onset differences.

Therapeutic Drug Monitoring Implementation

Sampling strategy optimization collects specimens at appropriate times relative to dose administration based on specific questions being addressed, typically trough levels immediately before doses for most medications, but occasionally peak measurements or alternative timing for specific agents. Target range interpretation applies appropriate concentration goals based on indication, infection site, organism susceptibility, or disease severity rather than fixed ranges, particularly important for antimicrobials where targets may vary based on infection characteristics. Adjustment algorithm implementation modifies dosing

regimens systematically based on measured concentrations, patient response, and established pharmacokinetic principles rather than arbitrary changes when levels fall outside target ranges.

DRUG INTERACTIONS

Interaction Mechanism Classification

Pharmacokinetic interactions affect drug absorption, distribution, metabolism, or elimination, altering medication concentrations without changing inherent pharmacological effects. Common examples include enzyme inhibition (ketoconazole increasing tacrolimus levels), enzyme induction (rifampin decreasing warfarin effect), protein binding displacement (valproic acid increasing free phenytoin), transporter effects (cyclosporine affecting statin disposition), and absorption alterations (calcium binding tetracyclines). Pharmacodynamic interactions involve drugs affecting the same physiological system with additive, synergistic, or antagonistic effects without altering concentrations. Examples include increased bleeding risk with combined anticoagulants and antiplatelets, enhanced QT prolongation with multiple QT-prolonging agents, and beta-blocker antagonism of beta-agonist bronchodilators.

Clinical Significance Assessment

Severity evaluation categorizes potential outcomes ranging from minor effects requiring monitoring to life-threatening consequences necessitating complete avoidance, with consideration of patient-specific risk factors potentially increasing vulnerability to particular interactions. Evidence quality assessment examines interaction documentation foundation including well-controlled studies, case reports, theoretical predictions, or in vitro data, recognizing that management decisions should reflect the strength of supporting evidence rather than treating all reported interactions equally. Temporal considerations evaluate interaction onset timing based on mechanism, with enzyme inhibition often occurring rapidly while induction develops over days to weeks, and offset timing following discontinuation varying similarly based on underlying mechanism.

Table 9.2: Drug Interaction Mechanisms and Management

Interaction Type	Mechanism	Clinical Significance	Management
Pharmacokinetic (Absorption)	Chelation, pH alteration, P-glycoprotein effects, gastric motility changes	Magnitude of absorption change, therapeutic index, clinical consequences	Separation timing, administration adjustments, monitoring, dose adjustments
Pharmacokinetic (Distribution)	Protein binding displacement, tissue distribution changes	Displaced drug characteristics, free fraction effects, clinical relevance	Dose adjustments, enhanced monitoring, alternative agents
Pharmacokinetic (Metabolism)	Enzyme induction/inhibition (CYP450, UGT), competing pathways	Inhibition/induction potency, affected drug's therapeutic index, timeline	Dose adjustments, alternative pathway drugs, therapeutic monitoring
Pharmacokinetic (Excretion)	Transporter inhibition, pH effects, excretion competition	Excretion dependency, alternative pathways, clinical consequences	Dose adjustments, monitoring, alternative agents, renal function monitoring
Pharmacodynamic (Additive)	Similar or complementary effects at same or related targets	Combined effect magnitude, benefit vs. risk, therapeutic intent	Dose adjustments of one/both agents, enhanced monitoring, therapeutic intent
Pharmacodynamic (Antagonistic)	Opposing effects at same or functional targets	Therapeutic failure risk, clinical impact, antagonism degree	Separation if possible, alternative agents, efficacy monitoring
Pharmacodynamic (Synergistic)	Potentiated effects beyond simple addition	Safety margin, benefit vs. risk, intended vs. unintended	Dose reduction of one/both agents