Adverse Drug Reactions

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Adverse Drug Reactions

Definitions:

- **The WHO defines an adverse drug reaction (ADR) as " a response to a drug that is noxious and unintended and occurs at doses normally used in man for the prophylaxis, diagnosis or therapy of disease, or for modification of physiological function".**

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- The use of the phrase 'at doses normally used in man' distinguishes the noxious effect during normal medical use from the toxic effect caused by poisoning (over dose).
- There is no need to prove a pharmacological mechanism for any noxious response to be termed as ADR.

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- **The term "side effect" is distinct from ADR.**
- **A side effect is an unintended effect of a drug related to its pharmacological properties and can include unexpected benefits of treatment.**

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- **The WHO definition has been criticized for excluding the potential for contamination of the product (dosage form) and ADRs associated with pharmacologically inactive excipients in the product.**
- **The use of the term drug also excluded the use of complementary and alternative treatments such as herbal products.**

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- **In an attempt to overcome these issues, the following definition of ADR was proposed:**

  "A harmful or unpleasant reaction, resulting from the intervention related to the use of a medicinal product, which:

1. **predicts hazard for future administration.**
2. **warrants prevention or specific treatment.**
3. **requires alteration of dosage regimen.**
4. **requires withdrawal of the product.**

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- **It is also important to avoid confusion with the term "adverse drug event (ADE)".**
- **ADE is an adverse outcome that occurs after the use of the drug, but which may or may not be linked to this use.**
- **Therefore, all ADRs are ADEs, but not all ADEs will be ADRs.**

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- **ADE can be used when it is NOT possible to suggest a causal link between a drug treatment and an adverse outcome.**
- **The suspicion of a causal relationship between the drug and the adverse effect is central to the definition of an ADR.**

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Epidemiology of ADRs:

1. **ADRs are responsible for 2.6% - 6.5% of admissions to hospitals.**
2. **3.5-14.7% of inpatients develop ADRs.**
3. **2.3% of patients die as a result of ADRs.**
4. **In primary care, estimates of the incidence of ADRs range from 25-30%.**
5. **ADRs are the 4^{th} - 6^{th} leading cause of death in USA.**

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- **Stay in hospital for patients having ADR was ~ 20 days compared to ~ 8 days without ADRs, leading to escalation of cost.**

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Classification of ADRs:

- **Are useful for avoidance and management of ADRs.**

A. **Rawlins-Thompson classification: defined by the properties of the drug and the ADR.**

1. **Type A: normal but exaggerated (augmented) pharmacological effects of the drug. Predictable, dose-dependent, common (80% of all ADRs), preventable.**

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2. **Type B: abnormal (bizzare) effects not related to the pharmacological effects of the drug, such as hepatotoxicity of isoniazid, and allergic reactions. More serious, could be fatal, often discovered after marketing of the drug. Unpredictable.**
3. **Other types: see table.**

Table 5.1 Extended Rawlins–Thompson classification of adverse drug reactions

Type of reaction	Features	Examples
Type A: Augmented pharmacological effect	Common Predictable effect Dose-dependent Low morbidity Low mortality	Bradycardia associated with a beta-adrenergic receptor antagonist
Type B: Bizarre effects not related to pharmacological effect	Uncommon Unpredictable Not dose-dependent High morbidity High mortality	Anaphylaxis associated with a penicillin antibiotic
Type C: Dose-related and time-related	Uncommon Related to the cumulative dose	Hypothalamic pituitary–adrenal axis suppression by corticosteroids
Type D: Time-related	Uncommon Usually dose-related Occurs or becomes apparent some time after use of the drug	Carcinogenesis
Type E: Withdrawal	Uncommon Occurs soon after withdrawal of the drug	Opiate withdrawal syndrome
Type F: Unexpected failure of therapy	Common Dose-related Often cause by drug interactions	Failure of oral contraceptive in presence of enzyme inducer

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B. **The DoTS system: It is based on Dose relatedness, Timing and patient Susceptibility:**

- **Examines the various factors that both describe the reaction and that influence an individual patient susceptibility.**
- **It first considers the dose of the drug (ADRs are dose-related).**
- **Reactions are divided into:**

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1. **Toxic effects: Effects related to the use of the drug outside their usual therapeutic dosage.**
2. **Collateral effects: Effects occurring within the normal therapeutic use of the drug. They include reactions not related to the expected pharmacological effect of the drug or off-target reactions of the expected pharmacologic effect in other body systems.**

Adverse Drug Reactions

3. **Hyper-susceptibility reactions: Reactions occurring in sub-therapeutic doses in susceptible patients.**

- **The time course of a drug's presence at the site of action can influence the occurrence of ADR.**

a. **Rapid infusion of furosemide is associated with transient hearing loss and tinnitus.**

b. **A constant low dose of methotrexate is more toxic than equivalent intermittent bolus doses.**

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- **DoTS categorizes ADRs as:**

1. **Time-dependent reactions. Range from rapid and immediate reactions, to those that can be delayed.**
2. **Time-independent reactions. Occur at any time within the treatment period, regardless of the length of course.**

- **The last factor in DoTS is susceptibility which include factors like genetic predisposition, age, sex, altered physiology, disease, and drug interactions.**

Table 5.2 DoTS system of ADR classification

Dose relatedness	Time relatedness	Susceptibility
Toxic effects: ADRs that occur at doses higher than the usual therapeutic dose *Collateral effects*: ADRs that occur at standard therapeutic doses *Hypersusceptability reactions*: ADRs that occur at sub-therapeutic doses in susceptible patients	*Time-independent reactions*: ADRs that occur at any time during treatment. *Time-dependent reactions*: *Rapid reactions* occur when a drug is administered too rapidly. *Early reactions* occur early in treatment then abate with continuing treatment (tolerance). *Intermediate reactions* occur after some delay, but if reaction does not occur after a certain time, little or no risk exists. *Late reactions* risk of ADR increases with continued-to-repeated exposure, including withdrawal reactions. *Delayed reactions* occur some time after exposure, even if the drug is withdrawn before the ADR occurs.	Raised susceptibility may be present in some individuals, but not others. Alternatively, susceptibility may follow a continuous distribution – increasing susceptibility with impaired renal function. *Factors include*: genetic variation, age, sex, altered physiology, exogenous factors (interactions) and disease.

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Factors affecting susceptibility to ADRs:

1. **Age:**

Elderly patients:

- **are more prone to ADRs because of age-related decline in both metabolism and elimination of drugs from the body. They also have multiple co-morbidities and thus more prescribed drugs.**

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Children:

1. **Differ from adults in drug response.**
2. **Neonatal differences in body composition, metabolism, and other physiological parameters increase the risk of specific ADRs.**
3. **Higher body water content can increase the volume of distribution of water soluble drugs.**
4. **Reduced albumin may be associated of high free concentrations of highly protein-bound drugs.**

Adverse Drug Reactions

5. **Immature blood-brain barrier can increase sensitivity to morphine and other drugs.**

- **Differences in drug metabolism and elimination and end-organ responses can increase risk.**
- **Chloramphenicol, digoxin, and ototoxic antibiotics have higher risks of toxicity in the first weeks of life.**

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Older children and young adults:

- **are more susceptible to some ADRs:**

1. **Increased risk of extrapyramidal effects associated with metoclopramide.**
2. **Use of aspirin is restricted under age of 12 years because of association with Reye's syndrome.**
3. **Heightened probability of dosing errors and the relative lack of evidence for both safety and efficacy put children at high risk.**

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2. <u>Gender:</u>

- **Women may be more susceptible to ADRs.**
- **Some ADRs are more common in women than men:**

1) **Impairment of concentration and psychiatric adverse events associated with anti-malarial agent mefloquine.**
2) **Drug-induced *torsade de pointes*, may be because of their longer QTc interval compared to men.**

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3. <u>Co-morbidities and concomitant drug use:</u>

- **Reduction in hepatic and renal functions increase the risk of ADRs.**
- **Co-morbidities such as congestive heart failure, diabetes, and peripheral vascular, chronic pulmonary, rheumatological, hepatic, renal, and malignant diseases were strong predictors of readmissions for ADRs.**
- **This might be due to pharmacokinetic or pharmacodynamic changes in these diseases, or drug interactions due to multiple therapy.**

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4. **Ethnicity:**

- **This is related to ADRs due to inherited traits of metabolism, and environmental factors.**
- **There is increased risk of angioedema with the use of ACE-inhibitors in Africans.**
- **Increased susceptibility of whites and blacks to CNS adverse effects of mefloquine compared to Chinese and Japanese.**
- **Increased risk of myopathy after rosuvastatin in Asians.**

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5. **Pharmacogenetics:**

- **discussed before.**
- **Read it again – Required.**

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Immunological Reactions:

- **The immune system is able to recognize drugs as foreign leading to allergic reactions.**
- **Small molecules can bind to proteins to trigger an immune response, and larger molecules can trigger an immune response directly.**
- **The immune response is NOT related to the pharmacological action of the drug.**
- **Prior exposure to the drug is required.**

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- **Allergic reactions range from rashes, serum sickness and angioedema to life-threatening bronchospasm and anaphylaxis.**
- **Patients with a history of atopic or allergic disorders are at higher risk.**
- **Types of immunological reaction: see following table.**

Table 5.3 Classification of immunological (hypersensitivity) reactions

Classification	Mechanism	Symptoms/signs and examples
Type I (immediate)	Drug/IgE complex to mast cells release of histamine and leukotrienes.	Pruritis, urticaria, bronchoconstriction, angioedema, hypotension, shock, for example, penicillin anaphylaxis.
Type II (cytotoxic)	IgG and complement binding to (usually) red blood cell. Cytotoxic T-cells lyse the cell.	Haemolytic anaemia and thrombocytopaenia, for example, associated with cephalosporins, penicillins and rifampicin.
Type III (immune complex)	Drug antigen and IgG or IgM form immune complex, attracting macrophages and complement activation.	Cutaneous vasculitis, serum sickness, for example, associated with chlorpromazine and sulphonamides.
Type IV (delayed type)	Antigen presentation with major histocompatibility complex protein to T-cells and cytokine and inflammatory mediator release.	Usually occur after 7–20 days. Macular rashes and organ failure, including Stevens–Johnson syndrome and toxic epidermal necrolysis, for example, associated with neomycin and sulphonamides.

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Formulation Issues Contributing to ADRs.

- **Rare.**
- **In 2006, cough medicines made using glycerin contaminated with diethylene glycol, (from China), were responsible for deaths in Panama due to diethylene glycol poisoning.**
- **Episodes of diethylene glycol poisoning have been reportes in Nigeria, India, Argentina and Haiti.**

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- **Osmosin was a slow-release preparation of indomethacin which uses an osmotic pump to deliver the drug. It caused 36 fatal cases of gastointestinal bleedings, caused by tablets lodged against the mucosa of GIT, exposing it to high local concentrations of indomethacin.**
- **Change of the excipient in a phenytoin formulation lead to development of severe ADR including coma in previously stable patients.**

Adverse Drug Reactions

- In that case, calcium phosphate dihydrate was replaced with lactose. The first slows phenytoin absorption, while lactose increased it.
- Although excipients are considered inert substances, serious adverse reactions such as anaphylaxis and angioedema have been reported.
- Sweetners, flavours, coloring agents, and preservatives have all been associated with ADRs.

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Pharmacovigilance and Methods of ADR Detection:

- **Pharmacovigilance is defined as "the study of the safety of marketed drugs under the practical conditions of clinical use in large communities".**

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- **Pharmacovigilance is concerned with the detection, assessment and prevention of ADRs and other drug-related problems, in order to achieve rational and safe therapeutic decisions in clinical practice.**

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Spontaneous reporting:

- **Is one of the main method to collect data about ADRs, by people who make a connection between a drug and a suspected drug-induced event.**
- **It requires only a suspicion of a causal link between the drug the adverse event.**
- **Spontaneous reports should contain variable levels of information.**
- **Because re-challenge with the drug is un-ethical, few reports contain such information.**

Adverse Drug Reactions

Causality Assessment:

- **Causality is very difficult to prove in pharmacovigilance and a high degree of suspicion is all that is needed for "Regulatory Authority" action.**
- **The most common method of causality assessment in use is 'unstructured clinical assessment' called 'global introspection'.**
- **Studies have shown marked disagreement between experts.**

Table 5.4 WHO causality categories for ADRs

Category	Description
Certain	Pharmacologically definitive, with re-challenge if necessary
Probably/likely	Reasonable temporal relationship, unlikely to be attributed to disease processes or other drugs, with reasonable dechallenge response
Possible	Reasonable temporal relationship, but could be explained by concurrent disease or drugs. No information on withdrawal
Unlikely	Temporal relationship improbable, concurrent disease or drugs provide plausible explanation
Conditional/unclassified	An event which requires more data for assessment
Unassessable/ unclassifiable	An event that cannot be judged because of insufficient/contradictory information which cannot be supplemented or verified

Adverse Drug Reactions

- **A more standardized objective method to assess causality that reduce assessor bias is the "Naranjo algorithm".**
- **It uses a questionnaire, and points are added or subtracted based on responses to each question.**
- **The total score is then used to place assessment as: definite, probable, possible or doubtful.**

Table 1-2. Naranjo ADR Probability Scale

Question	Yes	No	Do Not Know	Score
1. Are there previous conclusive reports on this reaction?	+1	0	0	
2. Did the adverse event appear after the suspected drug was administered?	+2	-1	0	
3. Did the adverse reaction improve when the drug was discontinued or a specific antagonist was administered?	+1	0	0	
4. Did the adverse event appear when the drug was readministered?	+2	-1	0	
5. Are there alternative causes (other than the drug) that, on their own, could have caused the reaction?	-1	+2	0	
6. Did the reaction reappear when a placebo was given?	-1	+1	0	
7. Was the drug detected in the blood (or other fluids) in concentrations known to be toxic?	+1	0	0	
8. Was the reaction more severe when the dose was increased or less severe when the dose was decreased?	+1	0	0	
9. Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	+1	0	0	
10. Was the adverse event confirmed by any objective evidence?	+1	0	0	

Total Score	ADR Probability Classification
9	Highly Probable
5–8	Probable
1-4	Possible
0	Doubtful

Adapted with permission from: Naranjo CA, Busto U, Sellers EM, et al. A method for estimating the probability of adverse drug reactions. Clin Pharmacol Ther 1981;30:239-45.

Adverse Drug Reactions

Roles of Health Professionals:

- **Health professionals in this context are those who prescribe, supply, administer, monitor or advise on drug use.**

1. **Their fundamental role is ensuring drugs are used safely.**

- **All patient factors that predispose to ADRs should be taken into consideration, which include co-morbidities, concomitant drugs, renal and liver functions, and genetic predisposition.**

Adverse Drug Reactions

2. **It is invaluable to have information about patient's history of ADRs, to avoid in-appropriate re-use of drugs which previously have caused ADRs.**
3. **Documentation of identified ADRs.**

Adverse Drug Reactions

Identifying and assessing ADRs in Clinical Practice:

- **Must take into account the factors listed in the box of the next slide.**

Box 5.1 Factors that may raise or suppress suspicion of a drug-induced event (Shakir, 2004)

The *temporal relationship* between the exposure to the drug and the subsequent event
The *clinical and pathological characteristics of the event* – events which are known to be related to drug use, rather than disease processes
The *pharmacological plausibility* – based on the observer's knowledge of pharmacology
Existing information in published drug information sources – whether or not the event has been noted by others
Concomitant medication – which may be considered the cause of an event
Underlying and concurrent illnesses – may alter the event or be considered the cause of the event
De-challenge – disappearance of symptoms after dose reduction or cessation of therapy
Re-challenge – reappearance of symptoms after dose increases or recommencement of therapy
Patient characteristics and previous medical history – past history of the patient may colour the view of the event
The potential for *drug interactions*

Adverse Drug Reactions

Preventing ADRs:

- **The majority of ADRs are preventable, thus reducing cost and even death. (How?)**

1. **Checking previous ADR history.**
2. **Minimizing the use of drugs with high risk to develop ADRs.**
3. **Tailoring drug selection to individuals based on factors that predispose to ADRs.**

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4. **Rational prescribing.**
5. **Improved sharing of information about patients between health-care providers.**
6. **Monitoring Therapy:**

- **Monitoring the effect of drugs by measurement of serum concentration or by measurement of physiological markers is another method of reducing the risk of ADRs.**

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- **It has been estimated that 25% of preventable drug-related hospital admissions are caused by failure to monitor renal function and electrolytes.**
- **Clozapine used for management of treatment – resistant schizophrenia is associated of significant risk of agranulocytosis, that can be eliminated by mandatory monitoring of white blood cells.**

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- **Advice on monitoring should be clear, provide an evidence-based frequency of monitoring, and acceptable outcomes or values.**

7. **Explaining risks to patients:**

- **Patients have the right to receive understandable information about the potential for ADR, to enable them to make an informed decision**

Adverse Drug Reactions

Definition of serious adverse event:

1. **Results in death.**
2. **Is life-threatening (places the subject at immediate risk of death from the event as it occurred).**
3. **Results in inpatient hospitalization or prolongation of existing hospitalization.**
4. **Results in a persistent or significant disability/incapacity.**
5. **Results in a congenital anomaly/birth defect.**

Adverse Events Severity Classification

Rank	Definition
Mild	Causing no limitation of usual activities, the participant may experience slight discomfort
Moderate	Causing some limitation of usual activities, the participant may experience annoying discomfort
Severe	Causing inability to carry out usual activities, the participant may experience intolerable discomfort or pain

Adverse Effect Prevalence

Very common	**More than 1/10 of subjects.** **>10%**
Common	**More than 1/100 to less than 1/10.** **>1% - <10%**
Uncommon	**More than 1/1000 to less than 1/100.** **>0.1% - <1%**
Rare	**Less than 1/1000.** **< 0.1%**

Drug Interactions

Drug Interactions

- Are considered adverse drug reactions.
- An interaction occurs when the effects of one drug are altered by the co-administration of another drug, herbal medicine, food, drink or other environmental agents.
- Increased in importance because of the widespread use of poly-pharmacy (multiple drug use), non-prescription use of herbal and complementary medicines, and food- and drink – drug interactions.

Drug Interactions

- **Although rational use of more than one drug at a time can greatly benefit patients, adverse interactions are not uncommon, and may be catastrophic.**
- **Drug interactions are usually avoidable.**
- **The greater the number of drugs taken, the more likely there will be an interaction.**

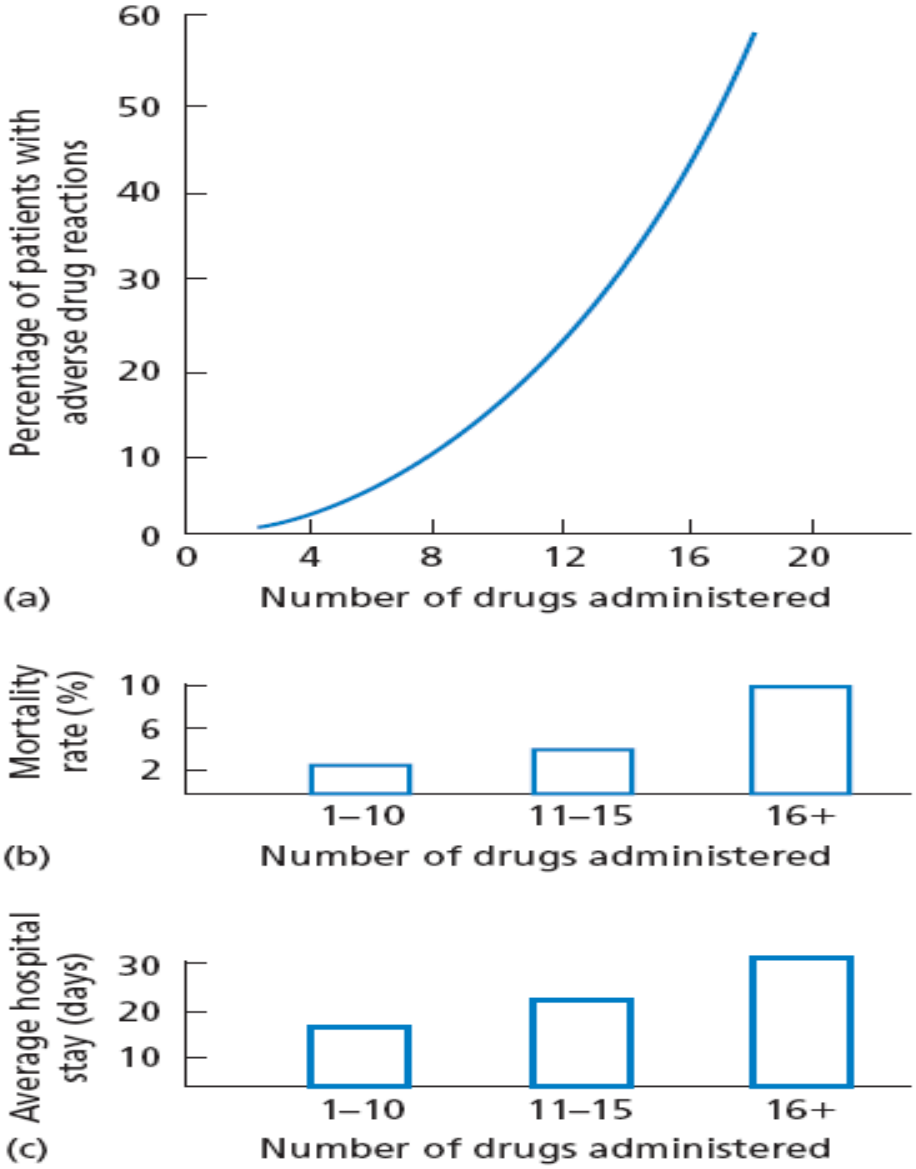


Figure 13.1: Relationship of number of drugs administered to (a) adverse drug reactions, (b) mortality rate and (c) average duration of hospital stay. (Redrawn by permission of the British Medical Journal from Smith JW et al. *Annals of Internal Medicine* 1966; 65: 631.)

Drug Interactions

Epidemiology:

- **It is difficult to obtain an accurate estimate of the incidence of drug interactions.**
- **In hospital in-patients, the incidence of drug interactions range from 1-2 %.**
- **In out-pateints, incidence of interactions ranged from 2-4 %.**
- **Other studies reported much higher incidence rates (7% and 22%, respectively).**

Drug Interactions

- **The frequency of such interactions is probably underestimated.**
- **Epileptic patients suffer from much greater rejection rates of transplants than non-epileptics, due to induction of the metabolism of immunosuppressant corticosteroids by antiepileptic drugs.**

Drug Interactions

Susceptible patients:

1. **Those with poly-pharmacy.**
2. **Those with hepatic or renal disease.**
3. **Those with long-term therapy for chronic diseases (HIV infection, epilepsy, diabetes, patients with intensive care, transplant patients, patients undergoing complicated surgical procedures.**
4. **Those with more than one prescriber.**
5. **Critically ill and elderly patients (altered homeostatic mechanisms).**

Drug Interactions

- **Many elderly individuals not uncommonly have several co-morbid conditions, needing several drugs.**
- **When a drug results in an adverse effect, it may be treated by another drug, which may add to the problem.**
- **Drug interactions can be: useful, of no consequence, or harmful.**

Drug Interactions

Useful Interactions:

A. Increased therapeutic effect:

- **Drugs can be used in combination to enhance their effectiveness.**
- **Disease is often caused by complex processes, and drugs that influence different components of the disease mechanism may have additive effects:**

1. An antiplatelet drug with a fibrinolytic in treating myocardial infarction.

Drug Interactions

2. **The use of a β_2 agonist with a glucocorticoid in the treatment of asthma to cause bronchodilation and suppress inflammation, respectively.**
3. **Drug resistance via synthesis of a microbial enzyme that degrades antibiotic (penicillinase-producing staphylococci) can be countered by using a combination of the antibiotic (amoxicillin) with an inhibitor of the enzyme (clavulanic acid).**

Drug Interactions

4. **Combinations of antimicrobial drugs are used to prevent the selection of drug-resistant organisms in tuberculosis.**
5. **Imipenem is partly inactivated by a dipeptidase in the kidney. This inactivation can e overcome by administering imipenem in combination with cilastin, a specific renal dipeptidase inhibitor.**

Drug Interactions

6. **The use of the combination of ritonavir and saquinavir in antiretroviral therapy.**

- **Ritonavir increases the systemic bioavailability of saquinavir by:**

a. **inhibiting its first-pass gastrointestinal effect (CYP3A).**

b. **inhibiting its fecal elimination by blocking the P-glycoprotein that pumps it back into the intestinal lumen.**

Drug Interactions

B. Minimize adverse effects:

- **Predictable adverse effects can sometimes be averted by the use of drug combinations.**

1. **Isoniazid neuropathy is caused by pyridoxine deficiency, and is prevented by the prophylactic use of this vitamin.**
2. **The combination of a peripheral dopa decarboxylase inhibitor (carbidopa) with levodopa permits reduction of dose of levodopa, while reducing the dose-related peripheral adverse effects (nausea and vomiting).**

Drug Interactions

C. Block acutely an adverse effect:

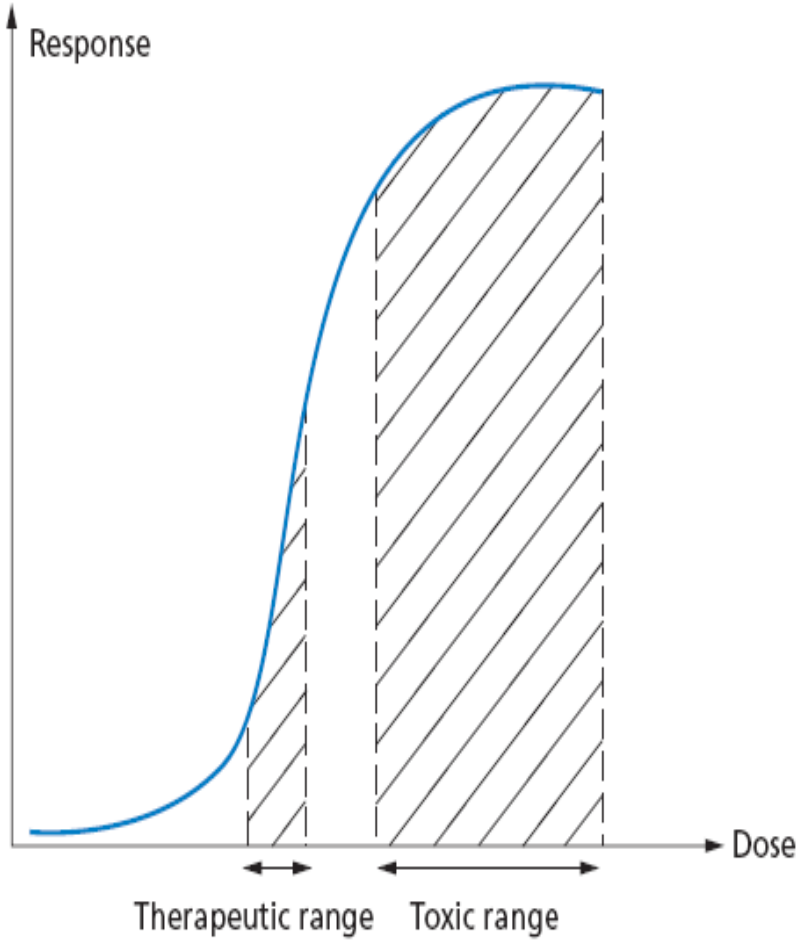
- **Drugs can be used to block an undesired or toxic effect:**

1. **A cholinesterase inhibitor to reverse neuromuscular blockade.**
2. **Naloxone to treat opioid overdose.**
3. **Vitamin K or fresh plasma to reverse the effect of warfarin.**

Drug Interactions

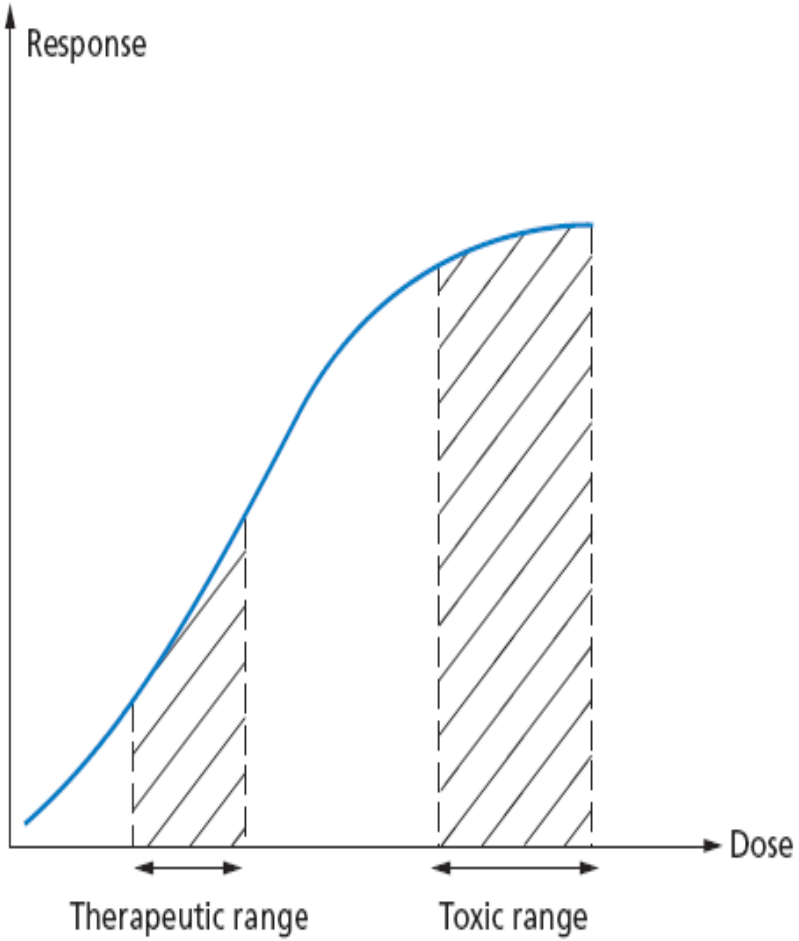
Harmful interactions:

- **It is impossible to memorize the many clinically important drug interactions, and prescribers should depend on suitable references to check for them.**
- **There are certain drugs with steep dose–response curves and serious dose-related toxicities for which drug interactions are especially liable to cause harm, and where special caution is required with concurrent therapy.**



Steep dose–response curve
Narrow therapeutic index

Adverse effect likely



Shallow dose–response curve
Wide therapeutic index

Adverse effect unlikely

Figure 13.2: Drug dose–response curves illustrating likelihood of adverse effect if an interaction increases its blood level.

Drug Interactions

Examples of drugs with high risk of interactions:

1. **Drugs with concentration-dependent toxicity: digoxin, lithium, aminoglycosides, cytotoxic agents, warfarin.**
2. **Drugs that the patient is dependent on their therapeutic effect: Immunosuppressants (cyclosporine, tacrolimus), glucocorticoids, oral contraceptives, antiepileptics, antiarrhythmics, antipsychotics, antiretrovirals…etc.**

Drug Interactions

3. **Drugs with steep dose-response curves: verapamil, sulfonyureas, levodopa.**
4. **Drugs with saturable hepatic metabolism: phenytoin. Why?**
5. **Monoamine oxidase inhibitors (antidepressants). Why?**

Drug Interactions

Severity of adverse drug interactions:

- **Adverse drug interactions are diverse:**
- **Unwanted pregnancy, from failure of the contraceptive pill due to concomitant medication, usually enzyme inducers.**
- **Hypertensive stroke, from hypertensive crisis in patients on monoamine oxidase inhibitors.**
- **Gastrointestinal or cerebral hemorrhage, in patients receiving anticoagulants (warfarin).**

Drug Interactions

- **Cardiac arrhythmias, secondary to interactions leading to electrolyte disturbances or prolongation of the QTc interval.**
- **Blood dyscrasias, from interactions between allopurinol and azathioprine.**

Drug Interactions

Mechanisms of drug interactions:

1. **Chemical (Pharmaceutical) interactions**
2. **Pharmacodynamic interactions**
3. **Pharmacokinetic interactions**

- **A drug interaction can result from one or a combination of these mechanisms.**

Chemical Interactions

- **Mainly these interactions occur outside the body if the drugs are mixed together before injection:**

1. **Inactivation of heparin with gentamicin.**
2. **Aminoglycosides and penicillins inactivate each other.**

- **Drugs may also interact in the lumen of the gut (tetracycline with iron, and colestyramine with digoxin and many other drugs).**

Table 13.1: Interactions outside the body

Mixture	Result
Thiopentone and suxamethonium	Precipitation
Diazepam and infusion fluids	Precipitation
Phenytoin and infusion fluids	Precipitation
Heparin and hydrocortisone	Inactivation of heparin
Gentamicin and hydrocortisone	Inactivation of gentamicin
Penicillin and hydrocortisone	Inactivation of penicillin

Pharmacodynamic Interactions

- **They are common.**
- **Most have a simple mechanism, consisting of summation or reduction of the effects of drugs with similar or opposing actions, respectively.**

Pharmacodynamic Interactions

1. **Drowsiness caused by an H_1-blocking antihistamine and alcohol.**

- **Patients must be warned of the dangers of consuming alcohol concurrently when antihistamines are prescribed, especially if they drive or operate machinery.**
- **Such interactions can be produced also by antidepressants, hypnotics, and some anti-epileptics leading to excessive drowsiness.**

Pharmacodynamic Interactions

2. **Antihypertensive drugs may be less effective by concurrent use of non-steroidal anti-inflammatory drugs, because of inhibition of biosynthesis of vasodilator prostaglandins in the kidney, and because of sodium and water retention.**
3. **β-blockers and verapamil may precipitate heart failure in patients with supra-ventricular tachycardia, because both have negative inotropic effects. The combination may also cause heart block and asystole.**

Pharmacodynamic Interactions

4. **Warfarin inhibits the coagulation cascade, whereas aspirin influences haemostasis by inhibiting platelet function.**

- **Therefore, the concomitant use of these drugs may cause excessive bleeding.**
- **Aspirin also predisposes to gastric bleeding by direct irritation and by inhibition of prostaglandin E_2 biosynthesis in the gastric mucosa.**

Pharmacodynamic Interactions

5. **One potentially important type of pharmacodynamic drug interactions involves the interruption of physiological control loops.**

- **The use of β-blocking drugs in patients with insulin-dependent diabetics deprive them of insulin-induced hypoglycemia warning signs, which are mediated by sensations initiated by activation of β-receptors.**
- **β-blockers, therefore, will mask the signs and symptoms of hypoglycemia.**

Pharmacodynamic Interactions

6. **Alterations in fluid and electrolyte balance represent an important source of pharmacodynamic drug interactions.**

- **Combined use of diuretics with actions at different parts of the nephron (indapamide or metolazone with furosemide) is valuable in the treatment of resistant edema, but such combination readily cause excessive intravascular fluid depletion, electrolyte loss, and "pre-renal" renal failure.**

Pharmacodynamic Interactions

- **Thiazide and loop diuretics commonly cause hypokalaemia, which increase the binding of digoxin to plasma membrane Na^+/K^+-ATPase, and hence digoxin toxicity is increased.**

Pharmacodynamic Interactions

7. **β_2-Agonists (salbutamol) also may reduce the plasma potassium concentration.**
8. **Conversely, potassium-sparing diuretics may cause hyperkalemia if combined with potassium supplements and/or angiotensin converting enzyme inhibitors (which reduce circulating aldosterone), especially in patients with renal impairment.**

- **Hyperkalaemia is one of the most common causes of fatal adverse drug reactions.**

Table 13.2: Interactions secondary to drug-induced alterations of fluid and electrolyte balance

Primary drug	Interacting drug effect	Result of interaction
Digoxin	Diuretic-induced hypokalaemia	Digoxin toxicity
Lidocaine	Diuretic-induced hypokalaemia	Antagonism of anti-dysrhythmic effects
Diuretics	NSAID-induced salt and water retention	Antagonism of diuretic effects
Lithium	Diuretic-induced reduction in lithium clearance	Raised plasma lithium
Angiotensin converting enzyme inhibitor	Potassium chloride and/ or potassium-retaining diuretic-induced hyperkalaemia	Hyperkalaemia

NSAID, non-steroidal anti-inflammatory drug.

Pharmacodynamic Interactions

9. **Antagonistic interactions:**

- **The bronchodilator action of selective β_2-agonists will be antagonized by β-blockers.**
- **The opioid antagonist naloxone blocks actions of opioids.**
- **Flumazenil blocks the action of benzodiazepines.**
- **Vitamin K blocks the action of oral anticoagulants (warfarin).**
- ***levo*-Dopa antagonizes the action of antipsychotics.**

Pharmacodynamic Interactions

10. **Neuroleptics and tricyclic antidepressants (TCAs) given with drugs producing electrolyte imbalance (diuretics) may cause ventricular arrhythmias.**
11. **Drugs that prolong the QTc interval if used concurrently can cause fatal polymorphic ventricular tachycardia (*torsade de pointes*).**
12. **Serotonin syndrome occur with combinations that affect serotonin. Selective serotonin reuptake inhibitors and MAOIs.**

- **Linezolid is an antibacterial with MAOI activity.**

Pharmacodynamic Interactions

12. MAOIs can prevent metabolism of tyramine in the gut which is taken up by adrenergic nerve terminals, releasing catecholamine and causing hypertensive crisis, fatal intracranial hemorrhage and cardiac arrest.

- **The effect is prolonged for several weeks until new MAO is synthesized (for irreversible inhibitors).**
- **The same applies to amphetamines [3,4-Methylenedioxymethamphetamine, MDMA (ecstasy)], phenylpropanolamine, and pseudoephedrine.**
- **Tyramine is found in cheese and red wine…**

Table 4.5 Examples of additive or synergistic interactions

Interacting drugs	Pharmacological effect
NSAID, warfarin, clopidogrel	Increased risk of bleeding
ACE inhibitors and K-sparing diuretic	Increased risk of hyperkalaemia
Verapamil and β-adrenergic antagonists	Bradycardia and asystole
Neuromuscular blockers and aminoglycosides	Increased neuromuscular blockade
Alcohol and benzodiazepines	Increased sedation
Pimozide and sotalol	Increased risk of QT interval prolongation
Clozapine and co-trimoxazole	Increased risk of bone marrow suppression

Pharmacokinetic Interactions

Absorption:

1. **Changes in gastric pH due to antacids, histamine H_2-antagonists, or proton pump inhibitors may affect weak acidic drugs absorption. The change affects the rate rather than the extent of absorption.**

- **Drugs affected include aspirin, ketoconazole, itraconazole.**

Pharmacokinetic Interactions

2. **Some drugs within the GIT form chelates that are not absorbed.**

- **Tetracyclines and fluoroquinolones can complex with iron, and antacids containing calcium, magnesium, and aluminium.**
- **Bisphosphonates are often co-prescribed with calcium supplements for treatment of osteoporosis and they reduce the bioavailability of each other, leading to therapeutic failure.**

Pharmacokinetic Interactions

3. **Adsorbents such as charcoal or kaolin, or anion-exchange resins (cholestyramine and colestipol) may reduce the absorption of many drugs (propranolol, digoxin, warfarin, TCAs, cyclosporine, *l*-thyroxine, ..).**

- **These effects can be avoided or reduced if an interval of 2-3 hours is allowed between administration of interacting drugs (spacing of drug administration).**

Pharmacokinetic Interactions

4. **Drugs that affect the rate of gastric emptying can affect absorption of other drugs absorbed in the upper part of the small intestine.**

- **Drugs with anticholinergic effects (TCAs, phenothiazines and antihistamines) decrease gut motility and reduce gastric emptying.**
- **This can decrease or increase absorption of drugs. (How?)**

Pharmacokinetic Interactions

- ✓ **TCAs can increase dicoumarol absorption as a result of increasing the time available for its dissolution and absorption.**
- ✓ **Anticholinergics reduce the bioavailability of levodopa, as a result of increased metabolism in the intestinal mucosa.**

Pharmacokinetic Interactions

- ✓ **Opioids strongly inhibit gastric emptying and greatly reduce the absorption rate of paracetamol, without affecting the extent of absorption.**
- ✓ **Metoclopramide increases gastric emptying and increases the absorption rate of paracetamol, propranolol, mefloquine, lithium and cyclosporine.**

Pharmacokinetic Interactions

5. **Induction or inhibition of drug transport proteins: Drugs that inhibit P-glycoprotein such as verapamil may increase bioavailability of digoxin, and thus its toxicity.**
6. **Malabsorption:**

- **Neomycin may cause a malabsorption syndrome causing reduced absorption of drugs.**
- **Orlistat, an inhibitor of pancreatic lipases, reduces absorption of co-administerd fat-soluble drugs and vitamins.**

Pharmacokinetic Interactions

Metabolism:

- **Is the most important target of drug interactions.**

A. Enzyme inhibition:

- **The time-course is often more rapid than that for enzyme induction, since it depends on the presence of high-enough concentration of the inhibiting drug at the metabolic site.**
- **Enzyme inhibition is responsible for many clinically significant drug interactions.**

Pharmacokinetic Interactions

- ✓ **Concurrent administration of an enzyme inhibitor leads to reduced metabolism of the drug and an increase in its steady-state concentration.**
- ✓ **Enzyme inhibition appears to be dose-related.**
- ✓ **The inhibition effect will be seen faster when the inhibitor half-life is short, and will be delayed for drugs with long half-lives. (Why?)**

Pharmacokinetic Interactions

- ✓ **Such interactions are most likely to affect drugs with narrow therapeutic range such as: theophylline, phenytoin, cyclosporine, and oral anticoagulants.**
- ✓ **Erythromycin, an inhibitor of CYP3A4, if taken by a patient on carbamazepine may lead to carbamazepine toxicity due to inhition of its metabolism leading to higher concentration.**

Pharmacokinetic Interactions

- ✓ **Ritonavir (an enzyme inhibitor) in patients receiving sildenafil could increase plasma concentrations of sildenafil markedly.**
- ✓ **Grapefruit juice, an inhibitor of CYP3A4, can markedly increase the bioavailability of nifedipine and felodipine given orally.**

Pharmacokinetic Interactions

- **A single glass of grapefruit juice can cause inhibition of CYP3A for 1-2 days, while regular consumption may continuously inhibit enzyme activity.**
- **Other drugs involved include simvastatin, tacrolimus, and cyclosporine.**

✓ **Enzyme inhibition usually results in increased pharmacological effect, but when the affected drug is a pro-drug, a reduced pharmacological effect may result.**

Pharmacokinetic Interactions

- **Clopidogrel is metabolized to an active metabolite by CYP2C19 which is inhibited by a proton pump inhibitor (lansoprazole) leading to reduced effectiveness of clopidogrel.**

✓ **Xanthine oxidase is responsible for inactivation of 6-mercaptopurine, a metabolite of azathioprine. Allopurinol markedly potentiates these drugs by inhibiting xanthine oxidase.**

Pharmacokinetic Interactions

- ✓ **Theophylline is not inactivated by xanthine oxidase, but rather by several CYPs (CYP1A2).**
- **Theophylline has serious dose-related toxicities, which are increased by Inhibitors of the CYP450 system, such as cimetidine, ciprofloxacin, erythromycin and clarithromycin.**
- **Severe exacerbations in asthmatic patients are often precipitated by chest infections, so an awareness of these interactions before commencing antibiotic treatment is essential.**

Pharmacokinetic Interactions

- ✓ **Hepatic CYP450 inhibition also accounts for clinically important interactions with phenytoin (isoniazid) and with warfarin (sulfonamides).**
- ✓ **Non-selective monoamine oxidase inhibitors (phenelzine) potentiate the action of indirectly acting amines such as tyramine, which is present in a wide variety of fermented products (cheese, wine, ..).**

Pharmacokinetic Interactions

- **Clinically important impairment of drug metabolism may also result indirectly from hemodynamic effects rather than enzyme inhibition.**
- **Lidocaine is metabolized in the liver and the hepatic extraction ratio is high.**
- **Drugs that reduces hepatic blood flow (negative inotropes, β-blockers, H_2-blockers) will reduce hepatic clearance of lidocaine leading to its accumulation and toxicity.**

Table 13.4: Interactions due to CYP450 or other enzyme inhibition

Primary drug	Inhibiting drug	Effect of interaction
Phenytoin	Isoniazid	Phenytoin intoxication
	Cimetidine	
	Chloramphenicol	
Warfarin	Allopurinol	Haemorrhage
	Metronidazole	
	Phenylbutazone	
	Co-trimoxazole	
Azathioprine, 6-MP	Allopurinol	Bone-marrow suppression
Theophylline	Cimetidine	Theophylline toxicity
	Erythromycin	
Cisapride	Erythromycin	Ventricular tachycardia
	Ketoconazole	

6-MP, 6-mercaptopurine.

Box 4.2 Examples of enzyme inhibitors frequently implicated in interactions

Antibacterials
Ciprofloxacin
Clarithromycin
Erythromycin
Isoniazid
Metronidazole

Antidepressants
Duloxetine
Fluoxetine
Fluvoxamine
Nefazodone
Paroxetine
Sertraline

Antifungals
Fluconazole
Itraconazole
Ketoconazole
Miconazole
Voriconazole

Antivirals
Amprenavir
Indinavir
Nelfinavir
Ritonavir
Saquinavir

Cardiovascular drugs
Amiodarone
Diltiazem
Quinidine
Verapamil

Gastro-intestinal drugs
Cimetidine
Esomeprazole
Omeprazole

Antirheumatic drugs
Allopurinol
Azapropazone
Phenylbutazone

Other
Aprepitant
Bupropion
Disulfiram
Grapefruit juice
Imatinib
Propoxyphene
Sodium valproate

Table 4.3 Examples of interactions due to enzyme inhibition

Drug affected	Inhibiting agent	Clinical outcome
Anticoagulants (oral)	Ciprofloxacin Clarithromycin	Anticoagulant effect increased and risk of bleeding
Azathioprine	Allopurinol	Enhancement of effect with increased toxicity
Clopidogrel	Lansoprazole	Reduced anti-platelet effect
Carbamazepine Phenytoin Sodium valproate	Cimetidine	Antiepileptic levels increased with risk of toxicity
Sildenafil	Ritonavir	Enhancement of sildenafil effect with risk of hypotension

Pharmacokinetic Interactions

B. Enzyme induction:

- **The most powerful enzyme inducers are the antibiotic rifampicin and the antiepileptic drugs barbiturates, phenytoin and carbamazepine.**
- **Carbamazepine, and to a lessor extent barbiturates, can induce their own metabolism (autoinduction).**
- **Other inducers include cigarette smoking, chronic alcohol use, and the herb St John's wort.**

Pharmacokinetic Interactions

- **The effect develops over several days or weeks because it requires new protein synthesis.**
- **Similarly, the effect generally persists for the same time period after withdrawal of the inducing agent.**
- **Inducers with short half-life (rifampicin) will induce metabolism more rapidly than those with long half-life (phenytoin) because they reach steady-state concentrations more rapidly.**

Table 13.3: Interactions due to enzyme induction

Primary drug	Inducing agent	Effect of interaction
Warfarin	Barbiturates Ethanol Rifampicin	Decreased anticoagulation
Oral contraceptives	Rifampicin	Pregnancy
Prednisolone/ ciclosporin	Anticonvulsants	Reduced immunosuppression (graft rejection)
Theophylline	Smoking	Decreased plasma theophylline

Pharmacokinetic Interactions

- **Enzyme induction is dose-dependent, but can occur at any dose for some drugs.**
- **Enzyme induction usually results in reduced pharmacological effect of the affected drug.**
- **There is a risk of therapeutic failure in patients taking cyclosporine, tacrolimus, HIV-protease inhibitors, irinotecan, and imatinib when patients take St John's wort (for depression).**
- **If the drug has active metabolites, pharmacological effect may increase.**

Pharmacokinetic Interactions

- **The dose of the drug may need to be increased in the presence of the inducer to attain the therapeutic effect.**
- **Withdrawal of an inducing agent during continued administration of a second drug can result in a slow decline in enzyme activity, leading to an increase in drug concentration and emergence of delayed toxicity from the second drug. (The dose is NO longer appropriate).**

Pharmacokinetic Interactions

- **When a patient receiving warfarin receives treatment with an enzyme inducer for a new medical event, the dose of warfarin may need to be increased.**
- **When the inter-current problem is resolved and the inducing drug is discontinued and the patient is left with the larger dose of warfarin, bleeding may result from an excessive effect of warfarin days or weeks later, as the effect of the enzyme inducer gradually wears off.**

Table 4.2 Examples of interactions due to enzyme induction

Drug affected	Inducing agent	Clinical outcome
Oral contraceptives	Rifampicin	Therapeutic failure of contraceptives
	Rifabutin	Additional contraceptive precautions required
	Modafinil	Increased oestrogen dose required
Ciclosporin	Phenytoin Carbamazepine St John's wort	Decreased ciclosporin levels with possibility of transplant rejection
Paracetamol	Alcohol (chronic)	In overdose, hepatotoxicity may occur at lower doses
Corticosteroids	Phenytoin Rifampicin	Increased metabolism with possibility of therapeutic failure

Table 4.1 Examples of drug substrates, inducers and inhibitors of the major cytochrome P450 enzymes

P450 isoform	Substrate	Inducer	Inhibitor
CYP1A2	Caffeine Clozapine Imipramine Olanzapine Theophylline Tricyclic antide- pressants R-warfarin	Omeprazole Lansoprazole Phenytoin Tobacco smoke	Amiodarone Cimetidine Fluoroquinolones Fluvoxamine
CYP2C9	Diazepam Diclofenac Losartan Statins SSRIs S-warfarin	Barbiturates Rifampicin	Amiodarone Azole antifungals Isoniazid
CYP2C19	Cilostazol Diazepam Lansoprazole	Carbamazepine Rifampicin Omeprazole	Cimetidine Fluoxetine Tranylcypromine

	Substrate	Inducer	Inhibitor
CYP2D6	Amitriptyline Codeine Dihydrocodeine Flecainide Fluoxetine Haloperidol Imipramine Nortriptyline Olanzapine Ondansetron Opioids Paroxetine Propranolol Risperidone Thioridazine Tramadol Venlafaxine	Dexamethasone Rifampicin	Amiodarone Bupropion Celecoxib Duloxetine Fluoxetine Paroxetine Ritonavir Sertraline

	Substrate	Inducer	Inhibitor
CYP2E1	Enflurane Halothane	Alcohol (chronic) Isoniazid	Disulfiram
CYP3A4	Amiodarone Terfenadine Ciclosporin Corticosteroids Oral contra-ceptives Tacrolimus R-warfarin Calcium channel blockers Donepezil Benzodiazepines Cilostazol	Carbamazepine Phenytoin Barbiturates Dexamethasone Primidone Rifampicin St John's wort Bosentan Efavirenz Nevirapine	Cimetidine Clarithromycin Erythromycin Itraconazole Ketoconazole Grapefruit juice Aprepitant Diltiazem Protease inhibitors Imatinib Verapamil

Pharmacokinetic Interactions

Distribution:

- **Displacement from protein-binding sites results in increased free or unbound fraction temporarily, but it falls due to enhanced elimination or distribution (clearance).**
- **Therefore, there are only few clinically important interactions due to protein binding displacement, particularly for highly protein-bound drugs and those that are NON-restrictively eliminated especially when administered parenterally.**
- **Examples: Phenytoin, Lidocaine.**

Pharmacokinetic Interactions

- **Drugs whose hepatic extraction ratio exceeds their unbound fraction in plasma are non-restrictively eliminated.**
- **Drugs whose hepatic extraction ratio is smaller than their unbound fraction in plasma are restrictively eliminated.**

Pharmacokinetic Interactions

Elimination Interactions:

Renal Excretion: at the following levels:

1. **Changes in urinary pH: Weakly acidic drugs are ionized at alkaline pH, and thus, are unable to be reabsorbed. Therefore, making urine more alkaline enhances the excretion of acidic drugs. Conversely, the elimination of weak bases is enhanced in acidic urine.**

- **Change of urine pH can be used to enhance drug elimination in cases of poisoning (salicylates, amphetamine, etc).**

Pharmacokinetic Interactions

2. **Changes in active renal tubule excretion: Probenecid increases plasma concentrations of penicillins by delaying their renal excretion.**
- **Salicylates and other NSAIDs can cause life-threatening methotrexate toxicity by inhibiting this process.**
3. **Changes in renal blood flow: Inhibition of synthesis of vasodilator prostaglandins by NSAIDs increases serum lithium levels and thus toxicity.**

Table 13.5: Competitive interactions for renal tubular transport

Primary drug	Competing drug	Effect of interaction
Penicillin	Probenecid	Increased penicillin blood level
Methotrexate	Salicylates	Bone marrow suppression
	Sulphonamides	
Salicylate	Probenecid	Salicylate toxicity
Indometacin	Probenecid	Indometacin toxicity
Digoxin	Spironolactone	Increased plasma digoxin
	Amiodarone	
	Verapamil	

Pharmacokinetic Interactions

4. **Many diuretics reduce sodium reabsorption in the loop of Henle or the distal tubule. This leads indirectly to increased proximal tubular reabsorption of monovalent cations.**

- **In patients treated with lithium salts, increased proximal tubular reabsorption of lithium can lead to lithium accumulation and toxicity.**

Pharmacokinetic Interactions

5. **Digoxin excretion is reduced by spironolactone, verapamil and amiodarone, all of which can precipitate digoxin toxicity as a consequence. Several of these interactions are complex in mechanism, involving displacement from tissue binding sites, in addition to reduced digoxin elimination.**

Pharmacokinetic Interactions

6. **Biliary excretion and the entero-hepatic circulation:**

- **Antibiotics which eliminate gut flora reduce the metabolism of drug conjugates back into the parent drug and thus it is quickly lost from the body reducing its plasma concentration and its pharmacological effect.**
- **This results in therapeutic failure as occurs in patients taking oral contraceptive concomitantly with broad-spectrum antibiotics.**
- **Be careful, this interaction is NOT well recognized!!**

Pharmacokinetic Interactions

7. **Drug transporter proteins:**

- **P-glycoprotein acts as efflux pump in renal proximal tubules, hepatocytes, intestinal mucosa, pancreas and blood-brain-barrier.**
- **It exports drugs into urine, bile and intestinal lumen; and reduces drug accumulation in CNS, respectively.**

Pharmacokinetic Interactions

- **P-glycoproteins can be induced or inhibited by some drugs.**
- **Verapamil increases digoxin level and toxicity at this level.**
- **There is also some overlap between P-glycoproten and CYP3A4 substrates, inducers and inhibitors.**

Table 4.4 Examples of inhibitors and inducers of P-glycoprotein

Inhibitors	Atorvastatin Ciclosporin Clarithromycin Dipyridamole Erythromycin Itraconazole Ketoconazole Propafenone Quinidine Ritonavir Valspodar Verapamil
Inducers	Rifampicin St John's wort

Drug-food Interactions

- **Food can cause clinically important interactions via an effect on drug absorption and gastrointestinal motility:**

a) **Iron, antibiotics should NOT ideally be taken with food.**

b) **Tyramine and MAOIs.**

c) **Grapefruit juice and calcium-channel blockers (inhibit CYP3A4 and P-glycoprotein).**

d) **Cruciferous vegetables (Brussel sprouts, cabbage, broccoli) are inducers of CYP1A2.**

Drug-herb Interactions

- **Up to 24% of hospital patients report use of herbal remedies.**

1. **Extracts of *Glycyrrihizin glabra* (liquorice عرق السوس) used for peptic ulcers can cause interactions in patients taking diuretics and digoxin.**

- **It may exacerbate hypokalemia induced by diuretics and cause digoxin toxicity.**
- **It also causes sodium and water retention like aldosterone and exacerbate heart failure and edema, and antagonize antihypertensive drugs action.**

Drug-herb Interactions

- **Herbal products with antiplatelet activity include Borage (*Borago officinalis*), Bromelain (أناناس) (*Ananas comosus*), capsicum (الفليفلة), feverfew, garlic (الثوم), Ginkgo (*Ginkgo biloba*) and tumeric (الكركم) can increase the risk of bleeding when used with aspirin and other antiplatelet drugs.**
- **Enhancement of hypoglycemic effect by Asian ginseng.**
- **Enhancement of hypotensive effect by hawthorn (الزعرور).**

Drug-herb Interactions

- **Lowering of seizure threshold by evening primrose oil and *Shankapushpi*.**
- **St. John's wort (*Hypericum*) interactions – discussed.**
- **Take history of herbal product intake because patients usually will NOT volunteer this information.**

Therapeutic Drug Monitoring

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Department of Pharmacology

Therapeutic Drug Monitoring

- There are inter-individual differences in drug response, and even intra-individual differences at different times or circumstances.
- This variability results from two main domains:

1. Variation in absorption, distribution, metabolism or excretion (pharmacokinetics).
2. Variation at/or beyond tissue receptors or other macromolecular drug targets (pharmacodynamics).

Therapeutic Drug Monitoring

- There must be a continuous variable (biological response) that is readily measured and is closely linked to the desired therapeutic outcome of a drug, as a measure of monitoring.
- 'Surrogate (alternative) marker' is a measure of effect of a specific treatment that may correlate well with a real clinical endpoint.
- Monitoring is also needed to reduce the risk of a clinical event (stroke, heart attack, pulmonary embolism, etc.).

Therapeutic Drug Monitoring

- **For example, antihypertensive drugs are monitored by their effect on blood pressure, statins by their effect on serum cholesterol, oral anticoagulants by their effect on the international normalized ratio (INR).**
- **Some times, there is NO good continuous variable to monitor, especially for diseases with an unpredictable or fluctuating course.**

Therapeutic Drug Monitoring

- **Measuring drug concentrations in plasma or serum identifies only pharmacokinetic variability, and may usefully guide dose adjustment. (e.g: anticonvulsants).**
- **Measuring drug concentrations for use in this way is often referred to as 'therapeutic drug monitoring'.**

Therapeutic Drug Monitoring

Role of drug monitoring in therapeutics:

- **Measurement of drug concentrations is *sometimes* a useful complement to clinical monitoring to assist in selecting the best drug regimen for an individual patient.**
- **Measurements of drug concentrations in plasma are most useful when:**

Therapeutic Drug Monitoring

1. **There is a direct relationship between plasma concentration and pharmacological or toxic effect, and a therapeutic range has been established.**

- **Drugs that work via active metabolites, and drugs with irreversible actions, are unsuited to this approach.**
- **Tolerance also restricts the usefulness of plasma concentrations measurement.**

2. **Effect can NOT readily be assessed quantitatively by clinical observation.**

Therapeutic Drug Monitoring

3. **Inter-individual variability in plasma drug concentrations from the same dose is large (phenytoin).**
4. **The drug has a low therapeutic index (if the ratio of toxic concentration/effective concentration is < 4).**
5. **Several drugs are being given concurrently and serious interactions are anticipated.**

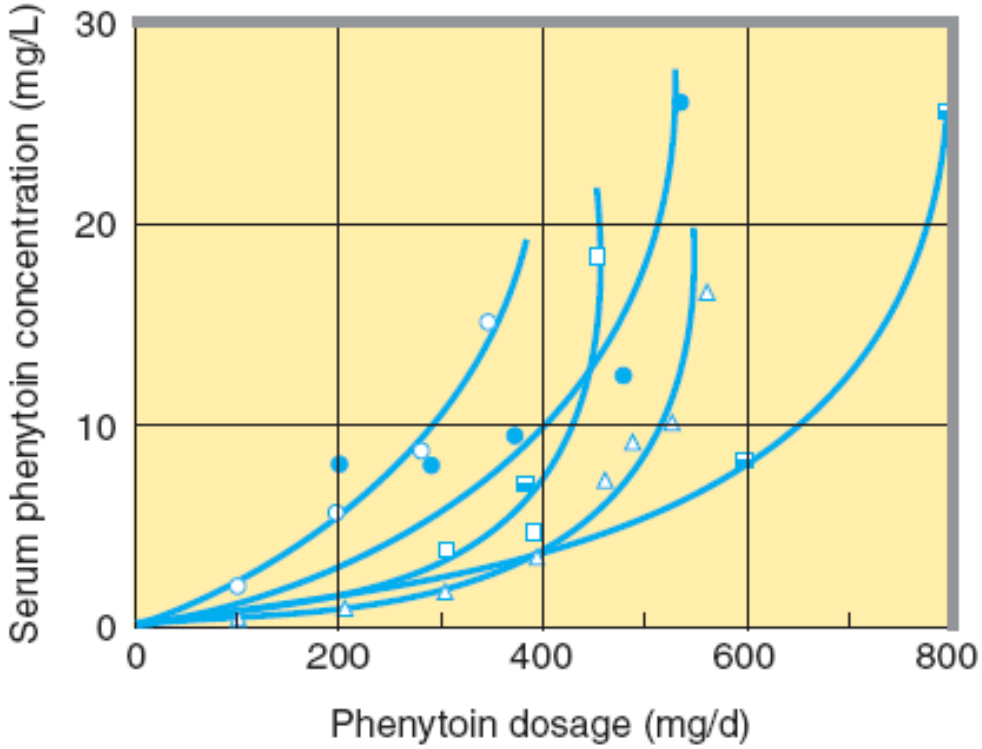


FIGURE 24–5 Nonlinear relationship of phenytoin dosage and plasma concentrations. Five patients (identified by different symbols) received increasing dosages of phenytoin by mouth, and the steady-state serum concentration was measured at each dosage. The curves are not linear, since, as the dosage increases, the metabolism is saturable. Note also the marked variation among patients in the serum levels achieved at any dosage. (Modified, with permission, from Jusko WJ: Bioavailability and disposition kinetics of phenytoin in man. In: Kellaway P, Peterson I [editors]: *Quantitative Analytic Studies in Epilepsy.* Raven Press, 1977.)

Therapeutic Drug Monitoring

6. **"Apparent resistance" to the action of a drug needs an explanation. (when non-compliance is suspected).**
7. **Another indication, distinct from therapeutic drug monitoring, for measuring drug concentrations in plasma is in clinical toxicology.**

- **Such measurements can guide management of a poisoned patient (paracetamol or aspirin).**

Therapeutic Drug Monitoring

Practical Aspects:

1. **Drug concentration at the site of action, which is related to drug effect, is proportional to plasma drug concentration.**
2. **A constant tissue to plasma drug concentration ratio only occurs during the terminal β-phase of elimination.**
3. **Earlier in the dose interval, the plasma concentration does NOT reflect the concentration at the site of action accurately.**

Therapeutic Drug Monitoring

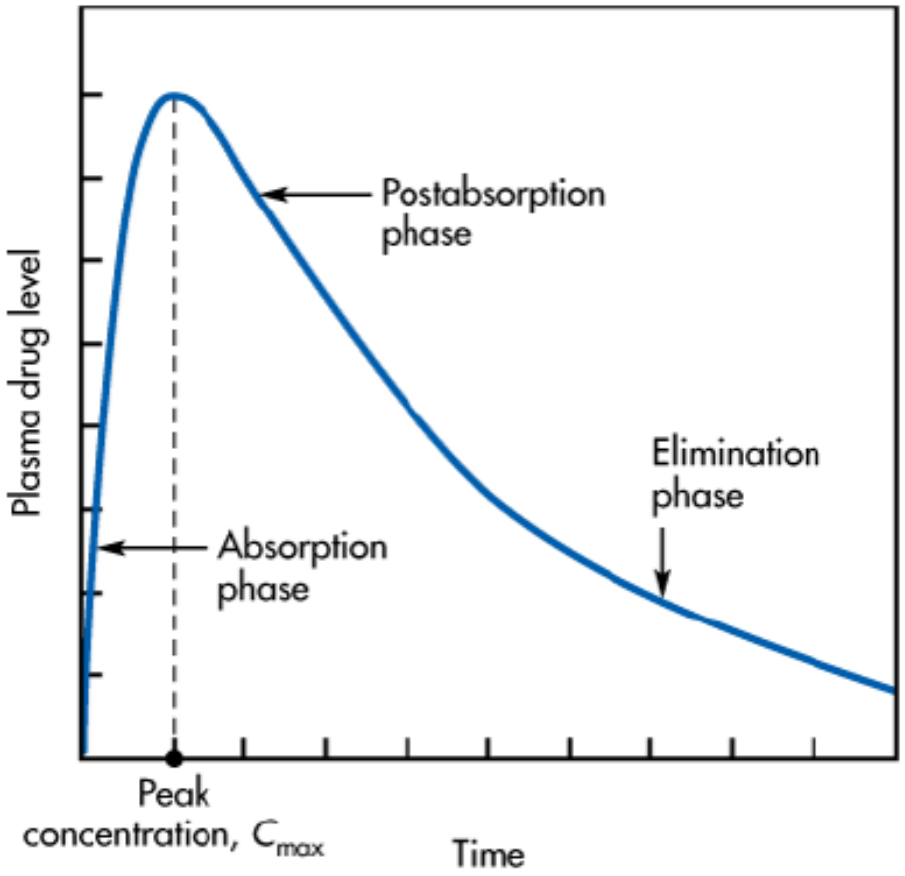
4. **Measurements must be made when distribution of the drug has been completed.**
5. **Timing of blood sampling is, therefore, critical for the measurement to be useful.**

- **There is No place for 'routine' or "random" blood samples for measurement of plasma drug concentration.**

6. **Sampling is only useful if the drug concentration in the body is at a "steady-state".**

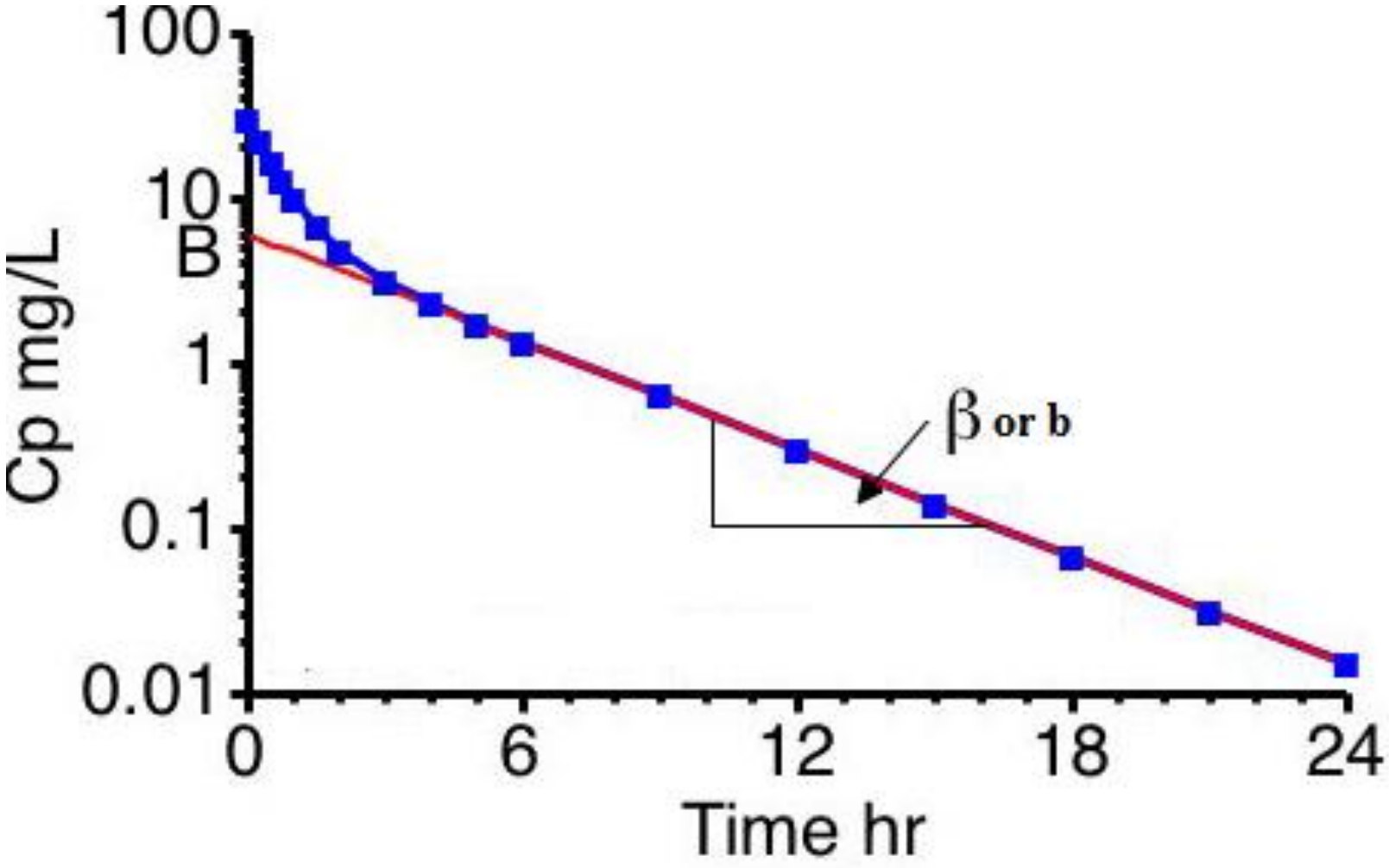
Therapeutic Drug Monitoring

7. **Usually during repeated dosing a sample is taken just before the next dose to assess the 'trough' concentration.**
8. **A sample may also be taken after distribution has been completed to determine the 'peak' concentration.**



Source: Shargel L, Wu-Pong S, Yu ABC: *Applied Biopharmaceutics & Pharmacokinetics, 6th Edition*: www.accesspharmacy.com

Plasma level–time curve for a drug given in a single oral dose. The drug absorption and elimination phases of the curve are shown.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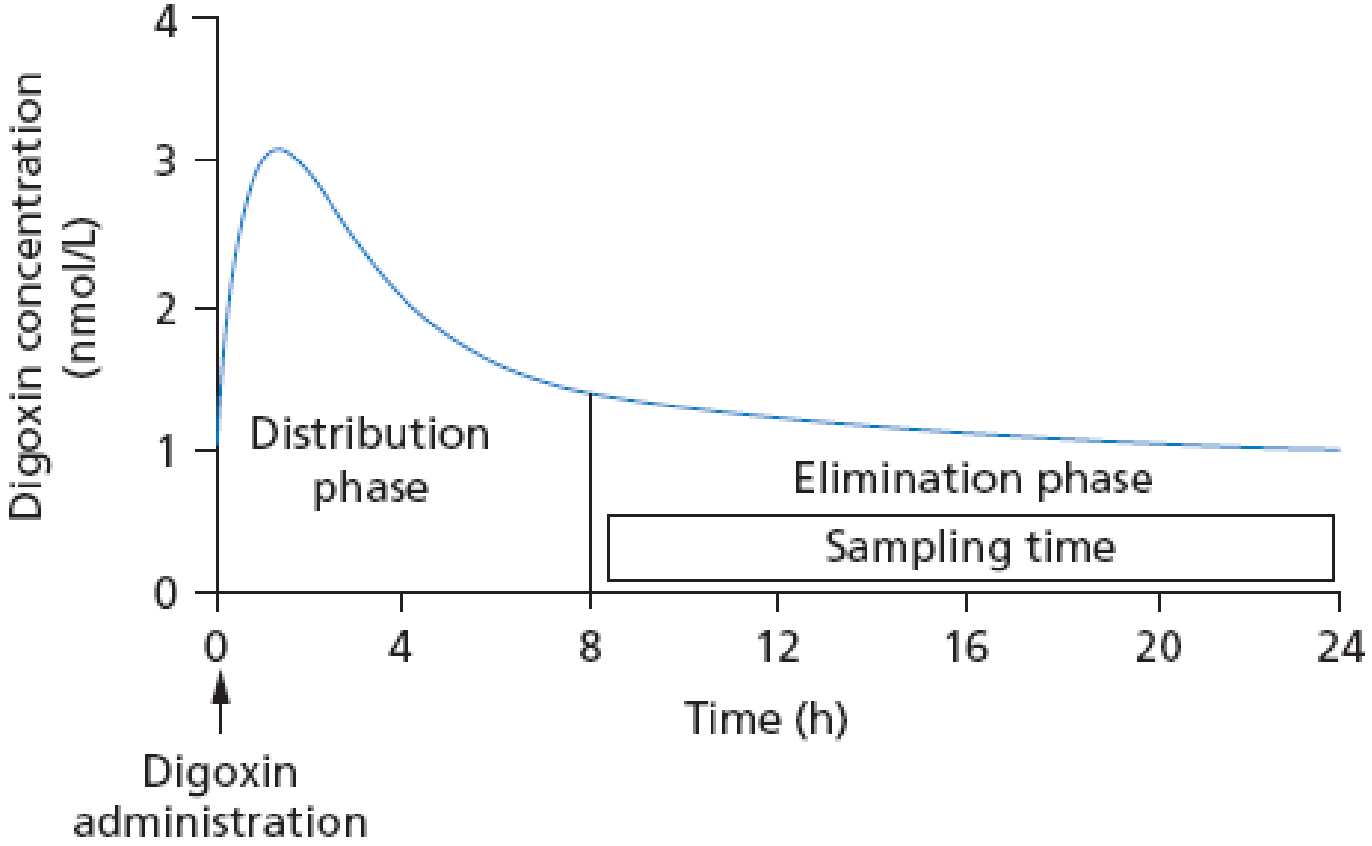
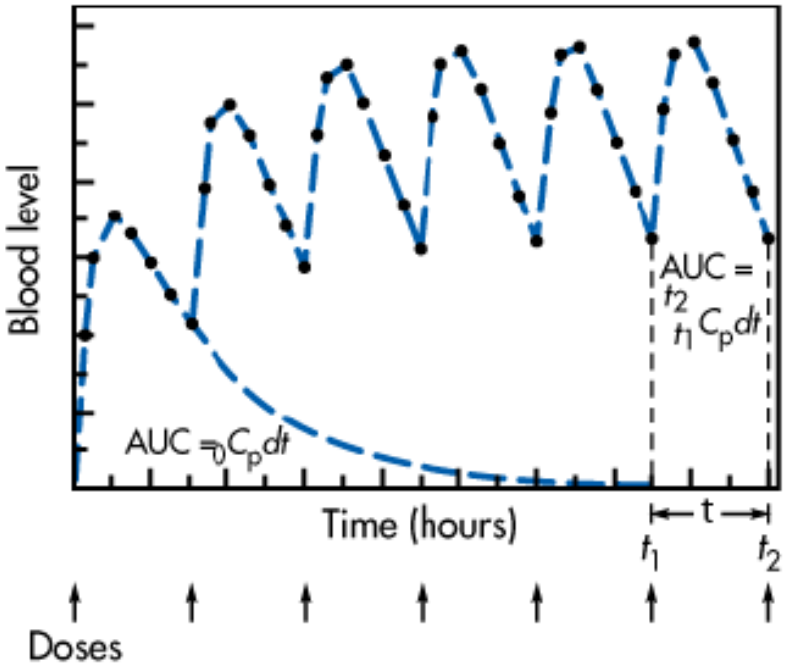
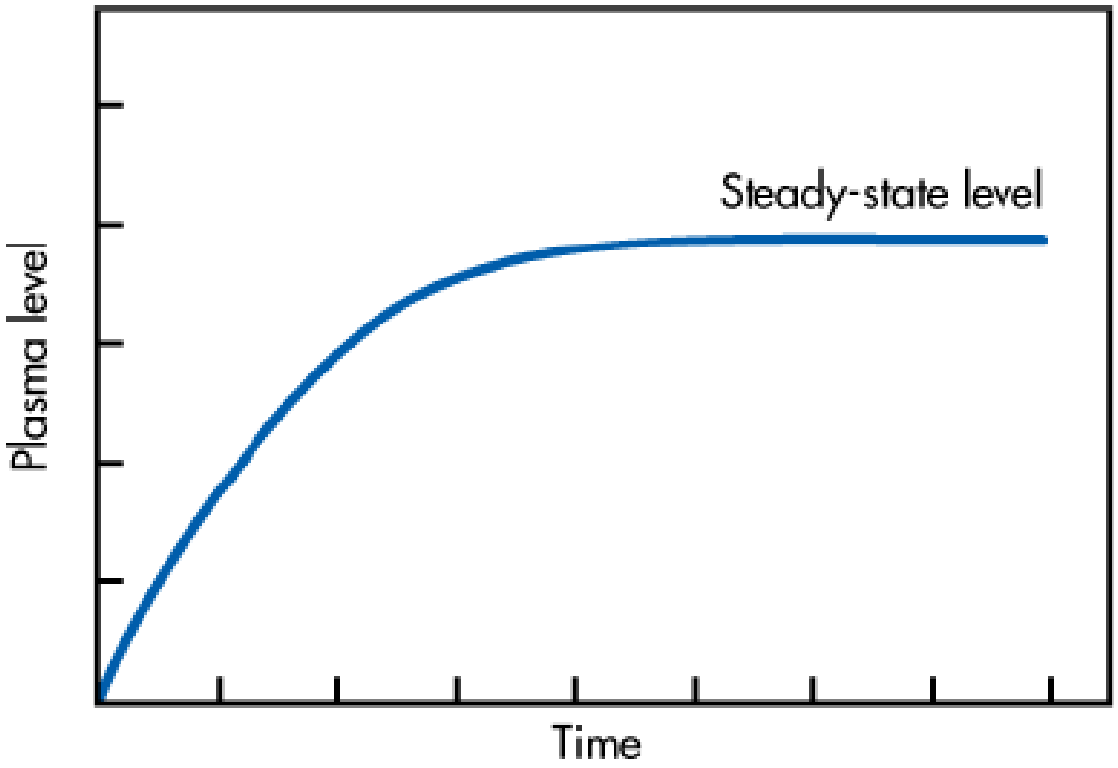


Figure 8.1: Serum concentration–time course following digoxin administration.



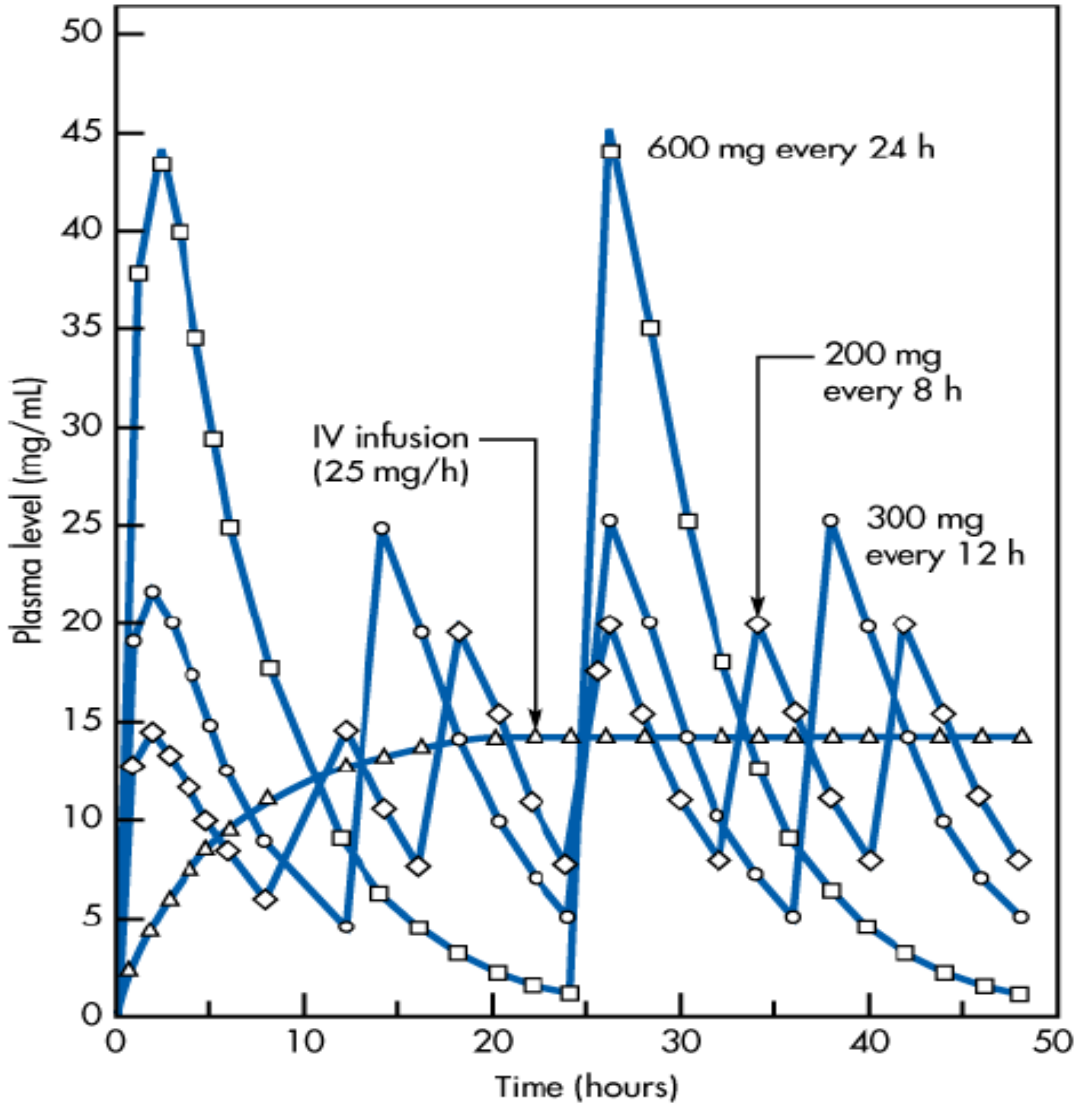
Source: Shargel L, Wu-Pong S, Yu ABC: *Applied Biopharmaceutics & Pharmacokinetics, 6th Edition*: www.accesspharmacy.com

Simulated data showing blood levels after administration of multiple doses and accumulation of blood levels when equal doses are given at equal time intervals.



Source: Shargel L, Wu-Pong S, Yu ABC: *Applied Biopharmaceutics & Pharmacokinetics, 6th Edition*: www.accesspharmacy.com

Plasma level–time curve for constant IV infusion.



Source: Shargel L, Wu-Pong S, Yu ABC: *Applied Biopharmaceutics & Pharmacokinetics, 6th Edition*: www.accesspharmacy.com

Simulated plasma drug concentration–time curves after IV infusion and oral multiple doses for a drug with an elimination half-life of 4 hours and apparent V_D of 10 L. IV infusion given at a rate of 25 mg/hr, oral multiple doses are 200 mg every 8 hours, 300 mg every 12 hours, and 600 mg every 24 hours.

Therapeutic Drug Monitoring

- **Advice on the interpretation of information obtained by measurement of serum drug concentration should be obtained from a local therapeutic drug-monitoring service, provided by clinical pharmacology and/or clinical pharmacy departments.**

Therapeutic Drug Monitoring

- **Plasma drug concentrations must always be interpreted in the context of the patient's clinical state.**
- **Random samples from patients to measure drug concentration are meaningless, misleading, as well as being a waste of time and money.**

Drugs For Which Therapeutic Drug Monitoring Is Used

Digoxin:

- **Measuring the plasma concentration can help optimize therapy, especially for patients in sinus rhythm where there is NO easy pharmacodynamic surrogate marker of efficacy.**
- **It is also useful in suspected toxicity or poor compliance.**
- **Before the introduction of digoxin monitoring, ~ 14% of all patients receiving digoxin showed evidence of toxicity, and this figure fell to ~ 6% following the introduction of monitoring.**

Drugs For Which Therapeutic Drug Monitoring Is Used

- **Optimum sampling time:**
  Trough (pre-dose) or > 8 h post-dose.
- **Time to steady state:**
  7-10 days.
- **Target range:**
  In AF: 0.8-2 µg/L.
  In heart failure: 0.5-1 µg/L.

Potential Interactions with Digoxin

Increase Serum Levels

- Amiodarone
- Benzodiazepines
- Bepridil
- Cyclosporine
- Diphenoxylate
- Indomethacin
- Itraconazole
- Macrolides
- Propafenone
- Propantheline
- Quinidine
- Quinine
- Spironolactone
- Tetracyclines
- Verapamil

Decrease Serum Levels

- Oral aminoglycosides
- Al^{+++}/Mg^{++}-containing antacids
- Antineoplastics
- Activated charcoal
- Cholestyramine
- Colestipol
- Kaolin/pectin
- Metoclopramide
- Neomycin
- Penicillamine
- Rifampin
- St. John's wort
- Sulfasalazine

Enhance Pharmacodynamic Effects

- Beta-blockers
- Calcium
- Verapamil
- Diltiazem
- Succinylcholine
- Sympathomimetics
- Diuretics

Antagonize Pharmacodynamic Effects

- Thyroid hormones

Drugs For Which Therapeutic Drug Monitoring Is Used

Lithium:

- **Optimum sampling time:** 12 h post-dose
- **Time to steady state:**

  3-7 days of chronic dosing
- **Target range:**

  Usually: 0.4-1 mmol/L.

  Elderly: 0.4-0.8 mmol/L.

  Acute bipolar disorder: up to 1.2 mmol/L.

Drugs For Which Therapeutic Drug Monitoring Is Used

Clozapine:

- **Optimum sampling time:**

  trough sample.
- **Time to steady state:**

  5-7 days of chronic dosing.
- **Target range:**

  ~ 350 µg/L, and clozapine/norclozapine ratio ~ 1.3

Drugs For Which Therapeutic Drug Monitoring Is Used

Aminoglycoside antibiotics:

- **Peak concentrations measured 30-60 minutes after dosing and trough levels, measured immediately before a dose.**
- **With extended interval aminoglycoside single daily dosing, a single drug concentration determined at a specified time after the completion of the distribution phase.**

Drugs For Which Therapeutic Drug Monitoring Is Used

Amikacin:

- **Optimum sampling time**:
  Peak (only used on divided-dose regimes):
  1 h post-dose (30-60 min after infusion complete)
  Trough: Immediately before next dose
  Time to peak 1 h
- **Time to steady state:** 10-15 h with normal renal function
- **Target range:**
  Trough: < 10 mg/L
  Peak: 20-30 mg/L.
  On once-daily dosing, target is a trough concentration of < 5 mg/L

Drugs For Which Therapeutic Drug Monitoring Is Used

Gentamicin, Tobramycin:

- **Optimum sampling time:**
  Peak: 1 h post-dose (30-60 min after infusion complete)
  Time to peak 1 h
  Trough: just before the next dose.
- **Time to steady state:**
  10-15 h with normal renal function
- **Target range:**
  Multiple dose regimes:
  Trough: < 2 mg/L
  Peak: 5-10 mg/L

Drugs For Which Therapeutic Drug Monitoring Is Used

Vancomycin:

- **Optimum sampling time:**
  Peak: 1 h post-dose (30-60 min after infusion complete)
  Trough: Immediately before next dose
  Time to peak 1 h
- **Time to steady state:**
  20-35 h with normal renal function
- **Target range:**
  Trough: 5-15 mg/L
  Peak: 20-40 mg/L

Drugs For Which Therapeutic Drug Monitoring Is Used

Teicoplanin:

- **Optimum sampling time:**

  Trough: Immediately before next dose
- **Time to steady state:**

  14 days or more
- **Target range:**

  Trough: 10-60 mg/L (15-60 mg/L in endocarditis, 20-60 mg/L for *Staphylococcus aureus)*

Drugs For Which Therapeutic Drug Monitoring Is Used

Phenytoin:

- **It is important to be aware of:**

1) **its non-linear pharmacokinetics**
2) **the possible effects of concurrent renal or hepatic disease on its pharmacokinetics**
3) **the possible effects of pregnancy on its distribution.**

- **Serum albumin concentration is necessary for appropriate interpretation of concentration.**

Drugs For Which Therapeutic Drug Monitoring Is Used

Phenytoin/Fosphenytoin

- **Optimum sampling time:**

1) In steady-state this is not too important because of long half-life of elimination.
2) A trough sample if on short-term fosphenytoin.

- **Time to steady state:**

  2-6 days of chronic dosing

- **Target range:**

  Total phenytoin: 5-20 mg/L

  Free phenytoin: 0.5-2 mg/L

Drugs For Which Therapeutic Drug Monitoring Is Used

Carbamazepine:

- **Optimum sampling time:**

  Pre-dose (trough sample)
- **Time to steady state:**

  2-6 days of chronic dosing
- **Target range:**

  4-12 mg/L

Drugs For Which Therapeutic Drug Monitoring Is Used

Ethosuximide:

- **Optimum sampling time:**

  Pre-dose (trough sample)

- **Time to steady state:**

  5-15 days of chronic dosing

- **Target range:**

  40-100 µg/L

Drugs For Which Therapeutic Drug Monitoring Is Used

Lamotrigine:

- **Optimum sampling time:**

  Before a dose (trough sample)
- Elimination half-life:

  20-35 h (shorter in children). ~ 15 h when given with enzyme inducers. ~ 60 h when given with valproate
- **Time to steady state:**

  5-7 days of chronic dosing
- **Target range:**

  < 24 mg/L

Drugs For Which Therapeutic Drug Monitoring Is Used

Valproate:

- **Optimum sampling time:**

  Before a dose (trough sample)

- **Time to steady state:**

  3-7 days of chronic dosing

  Protein binding ~95% (concentration dependent, decreasing binding above ~ 80 mg/L; also affected by endogenous metabolites)

- **Target range:**

  There is little evidence for the 50-100 mg/L range often cited, or the range of 50-125 mg/L cited for bipolar disorder monitoring.

  Plasma concentrations show poor correlation with effect.

Drugs For Which Therapeutic Drug Monitoring Is Used

Zonisamide:

- **Optimum sampling time:**

  Long half-life makes sampling time less critical in steady-state (however, sampling at trough is advised)

- **Time to steady state:**

  ~ 2 weeks of chronic dosing

- **Target range:**

  10-20 mg/L

Drugs For Which Therapeutic Drug Monitoring Is Used

Methotrexate:

- Plasma concentration is an important predictor of toxicity.
- Concentrations of 5 µmol/L 24 hours after a dose, or 100 nmol/L 48 hours after dosing, usually require folinic acid administration to prevent severe toxicity.

Drugs For Which Therapeutic Drug Monitoring Is Used

- **Optimum sampling time:**

  As required by protocol, often 24, 48 and (if necessary) 72 h post high-dose therapy.
- **Time to steady state:**

  1-2 days of chronic low dosing
- **Target range:**

  < 1 µmol/L 48 h post high-dose therapy or according to protocol.

Drugs For Which Therapeutic Drug Monitoring Is Used

Theophylline:

- **It has a narrow therapeutic index, and many factors influence its clearance.**
- **Measurement of plasma theophylline concentration can help to minimize toxicity (cardiac dysrhythmias or seizures).**
- **A therapeutic range of 5–20mg/L is quoted.**
- **(Plasma concentrations of 15mg/L are associated with severe toxicity in neonates due to decreased protein binding and accumulation of caffeine, to which theophylline is methylated in neonates, but not in older children).**

Drugs For Which Therapeutic Drug Monitoring Is Used

- **Optimum sampling time:**

  Trough: immediately before next dose

  Peak: 4-8 h post-dose (modified release preparations); 2 h post-dose (rapid-release)
- Time to peak 1-2 h post-dose (rapid-release) 4-8 h post-dose (modified release)
- **Time to steady state:**

  2-3 days (oral dosing, adults)
- **Target range:**

  10-20 mg/L

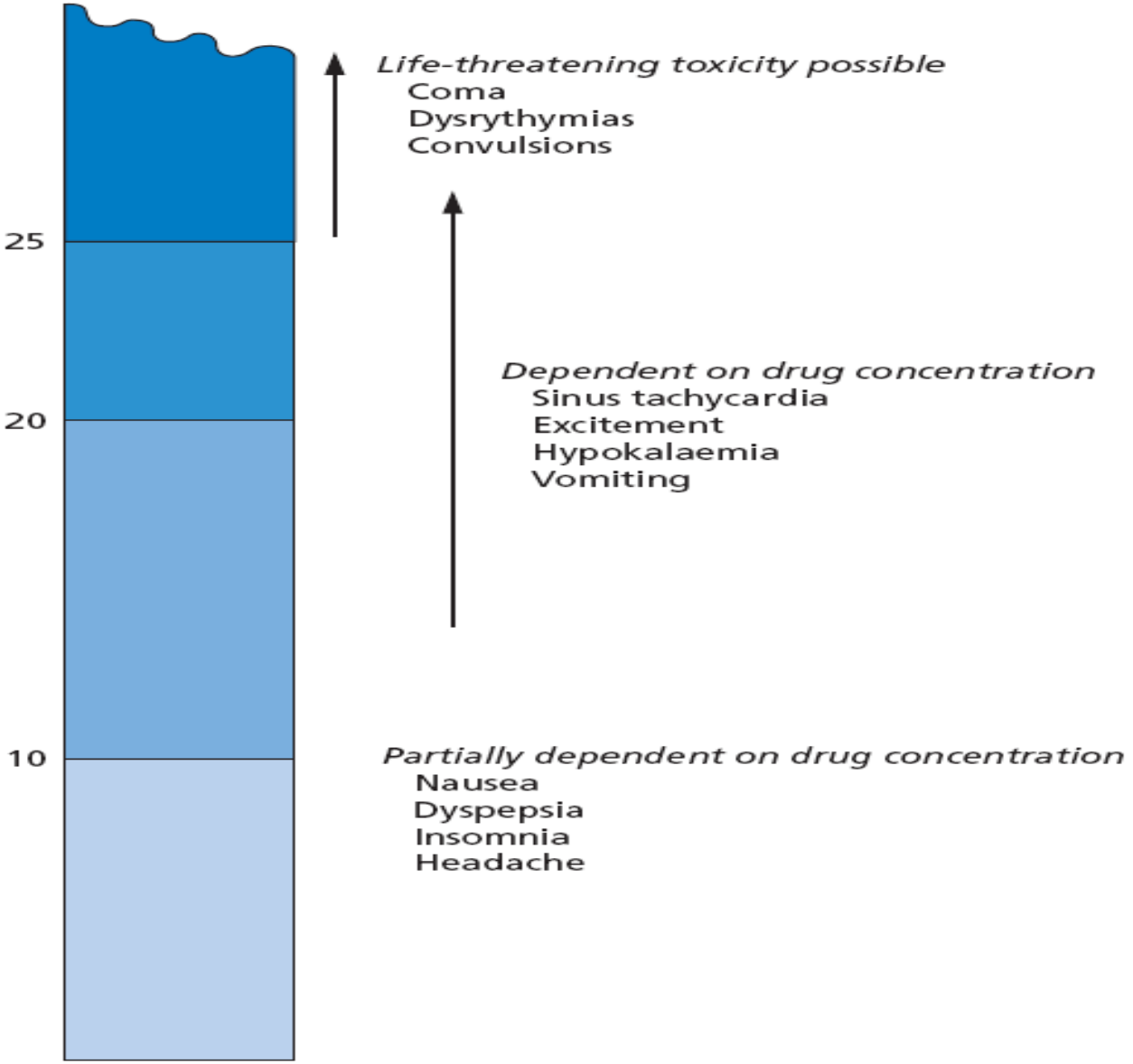


Figure 8.2: Theophylline plasma concentrations (mg/L). Note that there is a wide variation in the incidence and severity of adverse effects. (Adapted from Mant T, Henry J, Cochrane G. In: Henry J, Volans G (eds). *ABC of poisoning. Part 1: Drugs*. London: British Medical Journal.)

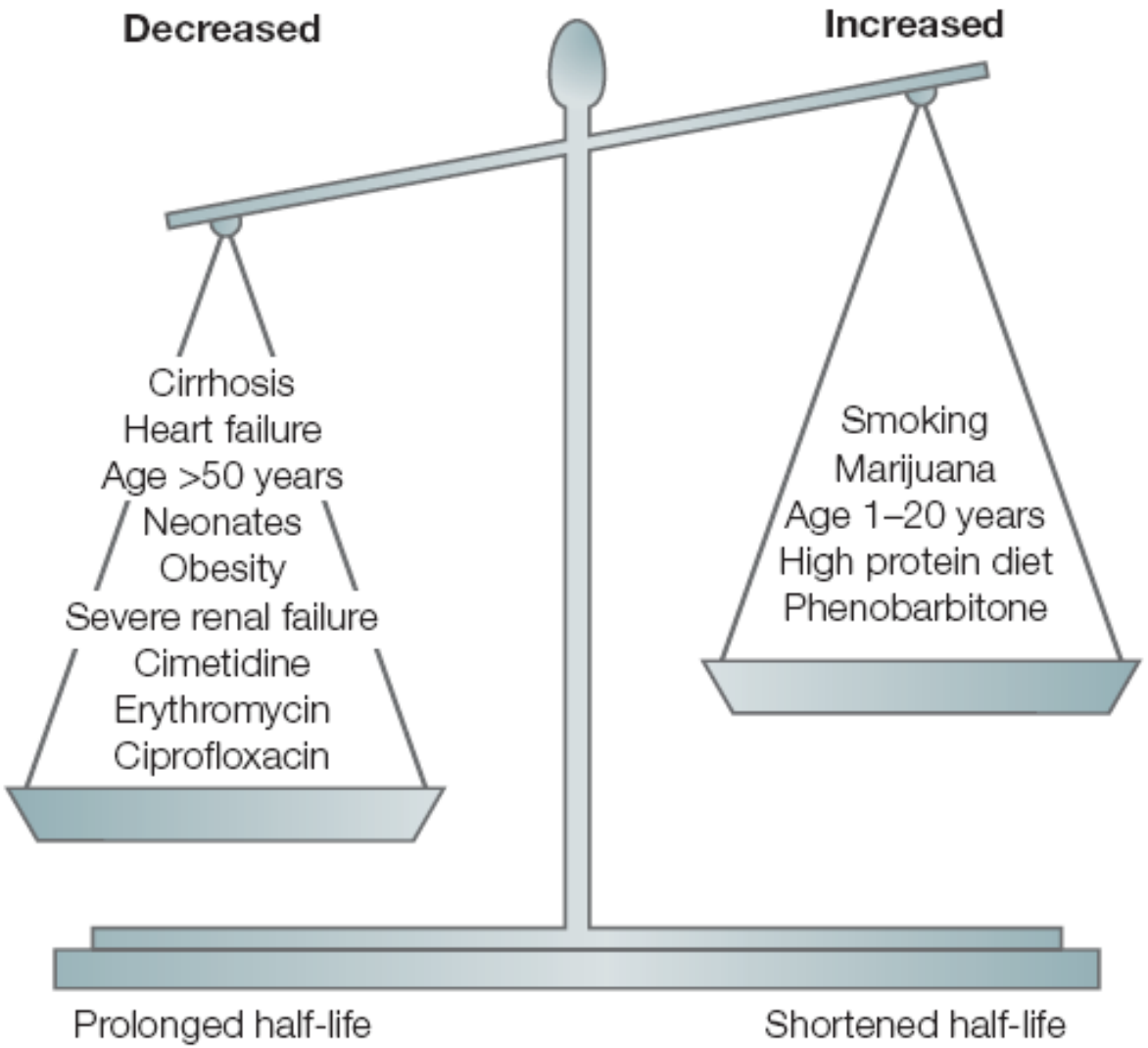


Figure 8.3: Theophylline clearance. (Adapted from Mant T, Henry J, Cochrane G. In: Henry J, Volans G (eds). *ABC of poisoning. Part 1: Drugs*. London: British Medical Journal.)

Some Drugs for which Therapeutic Drug Monitoring is Used

Immunosuppressants:

- **Cyclosporine compliance is a particular problem in children, and deterioration in renal function can reflect either graft rejection due to inadequate cyclosporine concentration or toxicity from excessive concentrations.**
- **Sirolimus use should be monitored, especially when used with cyclosporine or when there is hepatic impairment or during or after treatment with inducers or inhibitors of drug metabolism.**

Some Drugs for which Therapeutic Drug Monitoring is Used

Cyclosporine:

- **Optimum sampling time:**

  Trough (C_0) or 2 h post dose (C_2) whole blood sample.

- **Time to steady state:**

  2-6 days

- **Target range:**

  Varies widely with sample time, transplant type and time after transplantation

Some Drugs for which Therapeutic Drug Monitoring is Used

Sirolimus:

- **Optimum sampling time:**
  Trough (pre-dose) Whole blood sample
- **Time to steady state:**
  5-7 days
- **Target range:**
  With cyclosporine: 4-12 µg/L
  Off cyclosporine: 12-20 µg/L

Some Drugs for which Therapeutic Drug Monitoring is Used

Tacrolimus:

- **Optimum sampling time:**
  Trough (pre-dose) Whole blood sample
- **Time to steady state:**
  2-5 days
- **Target range:**
  Varies with sample time, transplant type and time after transplantation. Typically 15 µg/L following kidney transplantation, reducing to 5-10 µg/L

Some Drugs for which Therapeutic Drug Monitoring is Used

Mycophenolate:

- **Optimum sampling time:**
  Trough (pre-dose) or as needed to determine AUC
- **Time to steady state:**
  N/A
- **Target range:**
  Varies with transplant type, time of sample, method used and other medication

Some Drugs for which Therapeutic Drug Monitoring is Used

Antiarrhythmic drugs also require TDM

Drug Use During Lactation

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Pharmacology

Drugs in Lactation

- **Breast milk is the best form of nutrition for young infants.**
- **Mothers should breast feed exclusively for 6 months, and continue until at least 12 months while other foods are introduced.**
- **Breast milk provides all the energy and nutrients required for the first 6 months of life.**

Drugs in Lactation

Breast feeding provides:

1) **protection of the infant against gastric, respiratory, and urinary tract infections.**
2) **reduction in the rate of obesity, and juvenile-onset diabetes mellitus.**
3) **reduction in the rate of atopic diseases.**

- **Adults who were breastfed as infants have lower blood pressure and lower cholesterol levels.**

Drugs in Lactation

- **Maternal benefits include reduced risk of developing pre-menopausal breast cancer, and strengthening of the mother-infant bond.**
- **Breastfeeding mothers frequently require treatment with drugs.**
- **There are few contraindications to breast feeding.**
- **Some mothers may self-medicate with over-the-counter medications, nutritional supplements and herbal medicines.**

Drugs in Lactation

- **Nursing mothers need advice about safe drug use during lactation to protect the infant from drug-related adverse effects, and to allow necessary maternal treatment.**

Transfer of Drugs into Breast Milk

- **Most drugs pass to breast milk to some extent, but breastfeeding may be continued in most cases.**
- **The drug dose ingested by the infant via breast milk only rarely cause adverse effects.**
- **Almost all drugs enter milk by passive diffusion of un-ionized, protein un-bound drug through the lipid membrane of the alveolar cells of the breast.**

Transfer of Drugs into Breast Milk

- **Factors affecting rate and extent of passive diffusion include maternal plasma drug level, physiological differences between plasma and milk, and physicochemical properties of the drug.**
- **Milk differs from blood in having lower pH (ranges from 6.8 – 7.0 vs 7.4 in serum), less buffering capacity, and higher fat content.**

Transfer of Drugs into Breast Milk

Drug parameters affecting the extent of transfer into milk:

1. **pKa:**

- **It determines drug ionization at a given pH.**
- **Highly ionized drugs tend NOT to concentrate in milk.**
- **For basic drugs (erythromycin), a greater fraction will be ionized at an acidic pH, so that the milk compartment tends to trap weak bases.**

Transfer of Drugs into Breast Milk

- **Acidic drugs (penicillin) are more ionized at higher pH values and will be trapped in the plasma compartment.**
- **Drugs with higher pKa values generally have higher milk/plasma ratios.**

2. **Protein binding:**

- **Drugs that are highly bound to plasma proteins (warfarin) are likely to be retained in the plasma, because there is lower protein content in milk.**

Transfer of Drugs into Breast Milk

- **Milk concentration of highly plasma protein-bound drugs is usually low.**

3. **Lipophilicity:**

- **Water-soluble drugs will NOT effectively cross the alveolar epithelium of the breast.**
- **CNS-active drugs usually cross to breast milk.**

4. **Molecular weight:**

- **Drugs with low molecular weight (<200) readily pass into the milk through small pores in the cell wall of alveolar cells.**

Transfer of Drugs into Breast Milk

- **Drugs with higher molecular weights cross cell membranes by dissolving in the lipid layer.**
- **Protein molecules (very large molecular weights > 6000) are virtually excluded from milk.**

Transfer of Drugs into Breast Milk

- **Therefore, drugs that pass minimally to breast milk would be:**

1) **an acidic drug.**
2) **a drug with high plasma protein binding.**
3) **a drug with low-to-moderate lipophilicity.**

(most NSAIDs)

- **A basic drug, with low plasma protein binding and relative lipophilicity will achieve high concentration in breast milk (sotalol).**

Transfer of Drugs into Breast Milk

- In the first few days of life, large gaps exist between alveolar cells that permit enhanced passage of drugs into milk.
- By the end of the first week, the gaps close under the influence of prolactin.
- Colustrum is secreted in the first 2 days after birth and has high amounts of immunoglobulins, maternal lymphocytes, and maternal macrophages.

Transfer of Drugs into Breast Milk

- **Greater amounts of drugs are present in colustrum but the amounts received by infants are low because of the low volume of colustrum produced.**
- **Some drugs are pumped actively into breast milk, such as iodides, which pass into milk with high concentration.**

Assessing the Risk to the Infant

Many factors should be considered:

1. **Inherent toxicity of the drug: Antineoplastic drugs, radionuclides, and iodine-containing compounds would be of concern.**
2. **Multiple maternal therapy with drugs having similar adverse effects (anticonvulsants, and psychotropic drugs) will increase the risk for the infant.**

Assessing the Risk to the Infant

3. **Active metabolites (benzodiazepines) may prolong infant drug exposure and lead to drug accumulation.**
4. **Drugs with long half-lives (fluoxetine) may be problematic.**
5. **Gestational age: premature infants are more susceptible because of low clearance.**
6. **Maternal drug regimen: single doses or short courses have lower risk than chronic therapy or multiple medications.**

Reducing Risk to the Breastfed Infant

Strategies to reduce the risk of drugs in breast fed infants:

1. **Select medication considered safe for use in infants.**
2. **Give the maternal dose immediately after the infant has been fed, to avoid feeding at peak milk concentrations (if possible depending on frequency of feeding).**

Reducing Risk to the Breastfed Infant

3. If the mother is receiving a single dose of a hazardous material (radiopharmaceuticals), avoid breast feeding and resume after a reasonable washout period (5 half-lives). If the half-life is long, the washout period will be very long.
4. If the mother is using a once-daily medication, administration before the infant's longest sleep period may be advised to increase the interval to next feeding.

Reducing Risk to the Breastfed Infant

5. Breastfeeding mothers should avoid self-medication.
6. When drug use is indicated, the lowest effective dose should be used for the shortest possible period of time.
7. Simplify maternal regimen as much as possible.
8. New drugs are best avoided if a therapeutic equivalent is available for which data on safe use during lactation is available.

Reducing Risk to the Breastfed Infant

9. Infants exposed to drugs through breast milk should be monitored for side effects.
10. Select drugs with short half-lives and high protein binding to reduce accumulation.
11. For drugs taken multiple times per day, administration immediately after breast feeding provides the longest interval of back diffusion of the drug from breast milk into mother's serum.

Reducing Risk to the Breastfed Infant

12. During short-term drug therapy, and if the medication is NOT compatible with breastfeeding, the mother can pump milk out and discard it to preserve here milk-producing capability.

- Information regarding drug information on breastfeeding can be obtained from www.toxnet.nlm.nih.gov

Special Situations

Neonates and premature Infants:

1. They are at greater risk of developing adverse effects to drugs after exposure via breast milk.
2. Gastric emptying time is prolonged and may alter drug absorption.
3. Protein binding is decreased.
4. Total body water is higher.
5. Renal function is limited.

Special Situations

6. **Conjugation capacity is deficient (oxazepam, chloramphenicol).**

Glucose-6-phosphate dehydrogenase deficiency:

1. **It makes erythrocytes more susceptible to oxidative stress which results in hemolysis.**
2. **Only small amounts of the drug in breast milk are needed to produce hemolysis.**
3. **Breastfeeding should be avoided and alternative drugs should be used if the infant is G6PD deficient.**

Special Situations

Recreational Drug Use:

1. **Substances such as cannabis, LSD, and cocaine should be avoided during breastfeeding.**
2. **Chronic or heavy consumers of alcohol should NOT breastfeed.**

- **High intake of alcohol in breastfeeding mothers:**

a) **decrease milk let down.**

b) **disrupt nursing.**

c) **causes infant sedation, fluid retention, and hormone imbalances in infants.**

Special Situations

3. **Nicotine decreases basal prolactin production. Mothers should be encouraged NOT to smoke whilst breastfeeding.**
4. **Caffeine appears in breast milk rapidly after maternal intake. ~ 10 or more cups of coffee per day by the mother produce fussiness, jitteriness, and poor sleep patterns in breast fed infants. Preterm and newborn infants metabolize caffeine slowly and are at increased risk.**

Drug Effects on Lactation

1. **Drugs that affect dopamine activity are the main cause of effects on milk production.**

   A. Dopamine agonists (cabergoline) decrease milk production.

   B. Dopamine antagonists (domperidone) increase milk production.

2. **Early postpartum use of estrogens may reduce the volume of milk.**

- **Milk production can be abolished by the use of estrogens or oral contraceptives.**

Drug Effects on Lactation

- **Breast milk production can be increased by metoclopramide (10 mg po, 3 times daily for 7-14 days) if nonpharmacological means are ineffective. It stimulates prolactin secretion.**

Drug Effects on Lactation

Table 1. Pharmacological galactagogues

Oral pharmacological galactagogue	How it might work	Harms	Reference(s)
Domperidone	Peripherally acting dopamine D2-receptor antagonist, increases prolactin release from the pituitary gland	Headaches, somnolence, abdominal pain, diarrhoea. Increased risk of cardiac problems if history of prolonged Q-T interval, especially at high doses	Anderson 2013, Barone 1999, Doggrell 2014, Forinash 2012, Hale 2007, Zuppa 2010
Metoclopramide	Increases prolactin levels by anti-dopaminergic effects	Crosses the blood brain barrier causing restlessness, drowsiness, fatigue, depression and involuntary body movements	Anderson 2013, Forinash 2012, Hale 2007, Zuppa 2010

Drug Effects on Lactation

Table 2. Botanical galactagogues

Oral botanical galactagogue	How it might work	Harms	Reference(s)
Fenugreek (*Trigonella foenum-graecum*) نبات الحلبة	Increases milk flow by its phytoestrogens and diosgenin contents Stimulates sweat production, which would enhance milk secretion because the breast is a kind of sweat gland May stimulate milk production through dopamine receptor antagonism	Digestive upset, loose stools, light headedness, maple smell in the urine and sweat, mild allergic reaction. Possible peanut allergen cross sensitivity	Abascal 2008, Bingel 1994, Bruckner 1993, Capasso 2009, Humphrey 2007, Low Dog 2009, MacIntosh 2004, Mortel 2013, Romm 2010
Blessed thistle (*Cnicus benedictus*)	Stimulates the flow of blood to the mammary glands	Increased risk of bleeding	Abascal 2008, Bingel 1994, Zapantis 2012

Torbangun leaves (*Coleus amboinicus* Lour)	May stimulate proliferation of secretory mammary cells	Hypoglycaemia and stimulation of the thyroid gland	Bingel 1994, Zapantis 2012, Mortel 2013
Goat's rue (*Galega officinalis*)	Contains galegin, a precursor to metformin. May exert effects via contents of steroidal saponins Reputedly stimulates mammary growth	No data for humans. Minor abnormalities in blood and pathological specimens in rats	Abascal 2008, Bruckner 1993, Humphrey 2007, MacIntosh 2004, Rasekh 2008, Romm 2010
Fennel (*Foeniculum vulgare*) الشومر	Contains anethole, considered weakly estrogenic; may increase breast milk production or assist with the 'let-down' reflex. Reputedly stimulates mammary growth	Essential oil, may be toxic in large amounts	Abascal 2008, Bingel 1994, Bruckner 1993, Humphrey 2007, Low Dog 2009, Mills 2006, Mortel 2013, Romm 2010
Shatavari (*Asparagus racemosus*)	Estrogenic; may stimulate production by increasing prolactin. Increases weight of mammary gland in animal studies	Runny nose, itchy conjunctivitis, contact dermatitis and cough. May have laxative effect	Bingel 1994, Chaudhury 1983, Mortel 2013, Zapantis 2012

Drug Effects on Lactation

Anise or Aniseed *(Pimpinella anisum)* اليانسون	Contains anethole, considered weakly estrogenic; the aromatic compound in anise may act as a dopamine receptor antagonist	Possible allergen for some people	Abascal 2008, Bingel 1994, Bruckner 1993, Humphrey 2007, Low Dog 2009, Romm 2010
Milk thistle *(Silybum marianum)* الخرفيش	Appears to stimulate prolactin; possibly estrogenic	None known	Abascal 2008, Bingel 1994, Capasso 2009, Low Dog 2009, Mills 2006, Mortel 2013
Barley (*Hordeum vulgare*) الشعير	Polysaccharide stimulates prolactin	None known. Commonly consumed grain, also used to make beer	Bingel 1994, Humphrey 2007, Koletzko 2000, MacIntosh 2004, Sawagado 1988
Malunggay or Drumstick *(Moringa oleifera)*	Increases prolactin	None known. Commonly consumed as a vegetable in the Phillipines and elsewhere	Bingel 1994

Drugs Contraindicated during Lactation

Table 1-5. Agents Contraindicated During Lactation, Hazardous to Milk Production

Drug Class	Agents	Comments
Antiestrogens	Danazol GNRH agonists (e.g., leuprolide)	Ovarian suppression through pituitary-ovarian axis, inhibiting hormone production
	Anastrazole	Estrogen suppression through aromatase inhibition
Antiviral	Amantadine	Can suppress lactation by increasing dopamine
Dopamine agonists	Ropinirole Selegiline Rotigotine Dopamine	Lower serum prolactin concentrations, preventing lactation
Decongestants	Pseudoephedrine Propylhexedrine Phenylephrine	Oral intake can suppress milk production with single doses; topical application has a significantly lower risk unless overused
Ergots	Ergotamine Dihydroergotamine	Inhibit prolactin, preventing lactation
Ergot derivatives	Bromocriptine Cabergoline	Likely safe if treating hyperprolactinemia; otherwise contraindicated
Ethanol	Alcohol	Chronic ingestion will suppress milk production
Nicotine	Cigarettes	Decreased prolactin concentrations, reduced antioxidant properties of breast milk
Selective estrogen receptor antagonists	Tamoxifen Raloxifene	Inhibit estrogen effects in breast tissue

GNRH = gonadotropin-releasing hormone.

Drugs Contraindicated during Lactation

Table 1-6. Agents Contraindicated During Lactation, Hazardous to the Infant

Drug Class	Agents	Comments
Antiarrhythmic	Amiodarone	Several potential toxicities (e.g., pulmonary)
Anticholinergic	Dicyclomine	Contraindicated in infants < 6 months, apnea
Anti-infectives	Dapsone	Hemolytic anemia
	Rifabutin	Rash, suppression of white blood cells
	Flucytosine	Bone marrow suppression
	Foscarnet	Renal toxicity, seizures
CNS stimulants	Dextroamphetamine Amphetamines Methylphenidate	Not recommended; monitor infant for adverse events and appropriate weight gain
Cytotoxic agents	Antimetabolites, alkylating agents, etc Hydroxyurea	High potential of toxicity for the infant, including immunosuppression
Illicit substances	Cocaine, heroin, marijuana, etc.	High potential for significant toxicities in the infant

Drugs Contraindicated during Lactation

Immunosuppressants	Cyclosporine Tacrolimus	Not recommended; if used, monitor infant (for serum concentrations and adverse events)
	Everolimus Sirolimus	Not recommended until more information is available on these agents
	Mycophenolate	Not recommended, increase in infection rate
Leprostatic	Thalidomide	Several potential toxicities
Mood stabilizer	Lithium	High potential of toxicity in the infant, near therapeutic serum levels
Monoamine oxidase inhibitors	Isocarboxazid Phenelzine Selegiline Tranylcypromine	No information is available regarding these agents in breastfeeding. Other antidepressants are better options
Radioactive substances	I^{131}, etc.	Transfer of radioactive agents to the infant, destruction of thyroid tissue
Skeletal muscle relaxant	Tizanidine	Sedation, hypotension
Tetracyclines	Tetracycline Doxycycline Minocycline	Low penetration into milk, but therapy > 3 wk is not recommended due to potential of staining of teeth or changes in bone growth
Tricyclic agent	Doxepin	Significant sedation, respiratory depression
Vitamin A derivatives	Etretinate Isotretinoin	Excessive vitamin A intake and related toxicities, including liver damage and death

Drugs Use During Pregnancy

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Drugs use During Pregnancy

- **Most drugs move from the maternal circulation into the fetal circulation by diffusion.**
- **Some of them may attain high enough concentrations in the fetal circulation to be detrimental to the fetus.**
- **Reduction of maternal albumin, while fetal albumin is increased throughout pregnancy, may result in high concentration of certain protein-bound drugs in the fetus.**

Determining Drug Safety During Pregnancy

- **Pregnant women are NOT eligible to participate in clinical trials.**
- **Therefore, There is less than optimal sources to provide good quality of evidence for efficacy and safety of drugs during pregnancy (animal studies, case reports, case-control studies, prospective cohort studies, voluntary reporting ..).**
- **Thalidomide was found safe in animal studies, but teratogenic in humans.**
- **Thus, extrapolation of results of animal studies to humans is NOT always valid.**

Determining Drug Safety During Pregnancy

- **The available clinical studies suffer from bias (recall bias), and require large number of subjects.**
- **Assistance concerning teratogenicity of drugs can be obtained from some data bases:**

1. **WWW.motherisk.org**
2. **www.toxnet.nlm.nij.gov**

- **Pregnancy risk factors categories (A, B, C, D, X).**

Reasons for Drug Therapy During Pregnancy

1. Pregnancy-induced conditions such as nausea and vomiting, preeclampsia/eclampsia.
2. Chronic conditions diagnosed before pregnancy such as epilepsy, bronchial asthma, DM, hypertension etc..
3. Acute conditions that may occur during pregnancy such as infections, diabetes mellitus, hypertension, etc..

Reasons for Drug Therapy During Pregnancy

4. Fetal therapy:

- **Fetal therapeutics involves drug administration to the pregnant woman to benefit the fetus.**

A. **Corticosteroids are given to mothers to stimulate fetal lung maturation (surfactant) when preterm birth is expected.**

Reasons for Drug Therapy During Pregnancy

B. **Phenobarbital, when given to pregnant women near term, can induce fetal hepatic enzymes responsible for the glucuronidation of bilirubin.**

- **The incidence of jaundice is lower in newborns when mothers are given phenobarbital than when phenobarbital is NOT used.**

Reasons for Drug Therapy During Pregnancy

C. **Maternal use of zidovudine decreases transmission of HIV from the mother to the fetus.**

- **Combinations of three antiretroviral agents can eliminate fetal HIV infection almost entirely.**

Drug Therapy in Pregnancy

- **Most drugs taken by pregnant women can cross the placenta, although to variable concentrations.**
- **The developing embryo and fetus may be exposed to their pharmacologic, toxic and teratogenic effects.**

Factors Affecting Placental Drug Transfer

1. The physicochemical properties of the drug.
2. The duration of exposure to the drug.
3. Pharmacokinetics of the drug in fetal tissues.

Pharmacokinetics

A. Lipid Solubility:

- **Drug passage across the placenta is dependent on lipid solubility and the degree of drug ionization.**
- **Lipophilic drugs tend to diffuse readily across the placenta and enter the fetal circulation.**
- **Thiopental crosses the placenta almost immediately and can produce sedation or apnea in the newborn infant. Therefore, it should NOT be used for induction of anesthesia in case of cesarean section.**

Pharmacokinetics

- **Highly ionized drugs, such as tubocurarine, cross the placenta slowly and achieve very low concentrations in the fetus.**
- **Impermeability of the placenta to polar (or ionized) compounds is relative rather than absolute.**
- **If high enough maternal-fetal concentration gradients are achieved, polar compounds can cross the placenta in measurable amounts.**

Pharmacokinetics

- **Salicylate, which is almost completely ionized at physiologic pH, crosses the placenta rapidly, because the small amount of salicylate that is un-ionized is highly lipid-soluble.**

B. Molecular Size:

- **Drugs with molecular weights of 250–500 can cross the placenta easily.**
- **Drugs with molecular weights of 500–1000 cross the placenta with more difficulty.**

Pharmacokinetics

- **Drugs with molecular weights greater than 1000 cross very poorly.**
- **Heparin may be safely given to pregnant women who need anticoagulation. Because of its large size and polarity, it is unable to cross the placenta.**
- **Insulin is indicated for treatment of diabetes during pregnancy because it does NOT cross the placenta.**

Pharmacokinetics

C. pH

- **Maternal blood has a pH of 7.4 and that of fetal blood is 7.3.**
- **Therefore, weakly basic drugs with pKa above 7.4 will be more ionized in the fetal compartment, leading to ion trapping and, hence, to higher fetal blood levels.**

Pharmacokinetics

D. Placental Transporters:

- **Many drug transporters have been identified in the placental brush border membrane.**
- **P-glycoprotein transporter pumps back into the maternal circulation a variety of drugs, including anticancer drugs (vinblastine, doxorubicin) and other agents (anti-HIV drugs).**

Pharmacokinetics

E. Protein Binding:

- **Binding of drugs to plasma proteins (particularly albumin) may reduce the rate of transfer and the amount transferred.**
- **This might NOT be true if the drug is highly lipid soluble (thiopental used in induction of anesthesia). The transfer of such compounds will depend on placental blood flow.**

Pharmacokinetics

- **Fetal proteins have lower binding affinity than maternal proteins.**
- **This has been shown for sulfonamides, barbiturates, phenytoin, and local anesthetic agents.**
- **Very high maternal protein binding of glyburide is associated with lower fetal blood levels because it does not cross placenta. This drug is also effluxed from the fetal circulation.**

Pharmacokinetics

F. Placental and Fetal Drug Metabolism:

- **The placenta plays a role as a site of metabolism of some drugs passing through it.**
- **Pentobarbital is oxidized by the placenta.**
- **The metabolic capacity of the placenta may lead to formation of toxic metabolites (ethanol, benz(a)pyrenes).**
- **Some drugs that enter the fetal liver may be partially metabolized before reaching the fetal circulation.**

Effects of Drugs on the Product of Conception

There are several possibilities:

1. **No Effect.**
2. **Restricted growth.**
3. **Impairment of functional development.**
4. **Placental damage, Abortion & Death.**
5. **Neonatal problems.**
6. **Congenital malformations (Tertogenicity).**

Drug Selection During Pregnancy

- Most drugs are relatively safe during pregnancy, while some have the potential to be teratogenic.
- The baseline risk of congenital malformations is 3-6%.
- 3% of congenital malformations are severe.
- < 1% of congenital malformations are due to drugs.
- Genetic causes are responsible for 15-25% of cases.
- Maternal conditions and infections, and environmental factors account for 10% of cases.
- 65-75% of cases are idiopathic.

Causes of Congenital Malformations

1. X-Radiation (1920s).
2. UV radiation (skin cancer).
3. Viral Infections (Rubella) (1940s).
4. Drugs and chemicals (Thalidomide and limb deformities) (1960).

- Defects that can be avoided, should be avoided!

Causes of Congenital Malformations

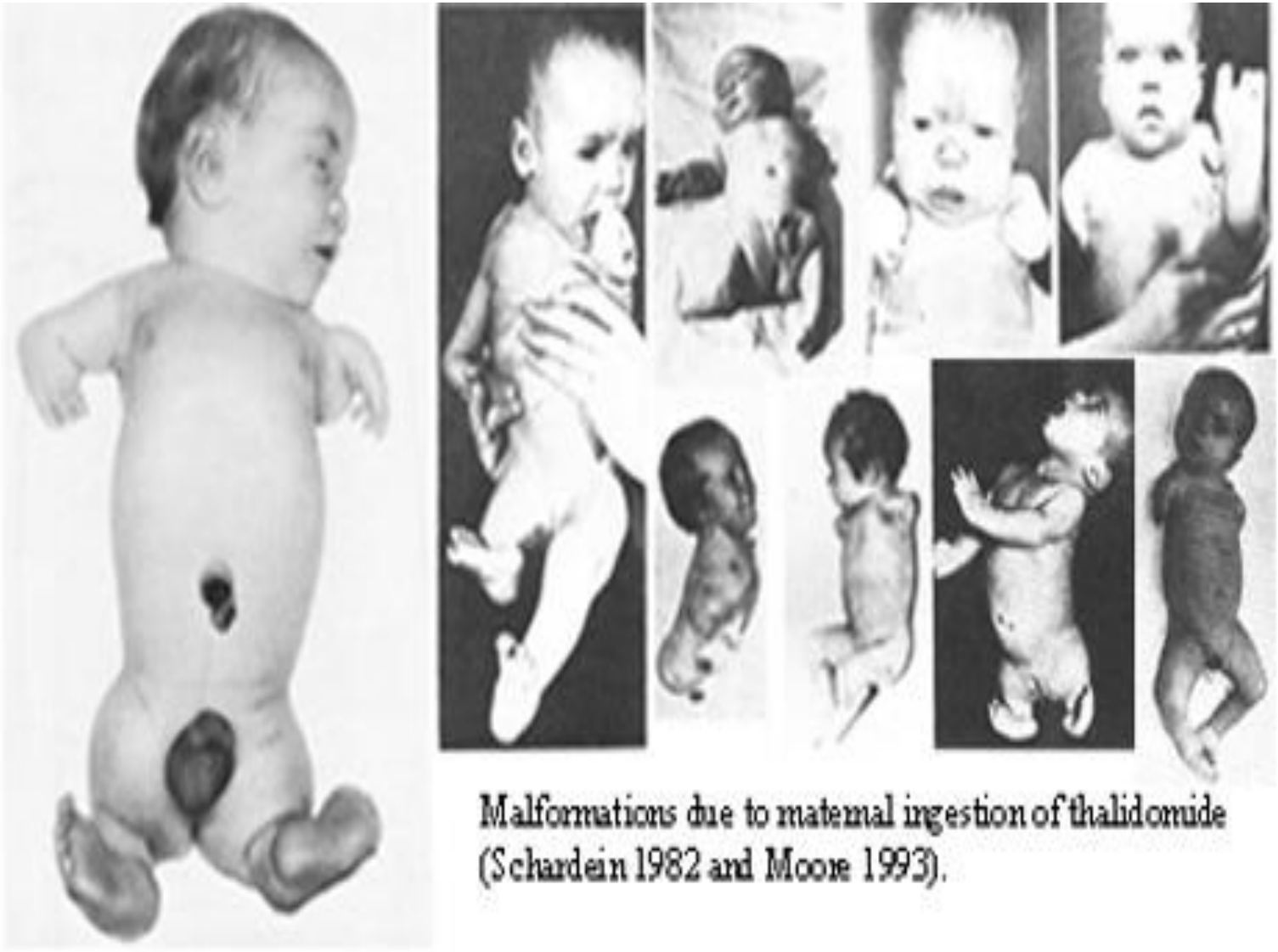
For more than 90% of available drugs, the human teratogenic risk is NOT determined. Why?

1. **Performance of drug experiments during human pregnancy to test for teratogenicity is unethical and prohibited.**
2. **Evidence to support teratogenesis is derived from animal studies.**

- **Dosage used in animals are much higher than therapeutic doses to women. Therefore, results in animals do not always extrapolate to humans.**

Teratogenic Drug Actions

- **A single intrauterine exposure to a drug, at a critical time during development, can affect the fetal structures undergoing rapid growth**
- **Types of anomalies are determined by the time of exposure during pregnancy.**
- **The thalidomide phocomelia risk occurs during the 4^{th}-7^{th} weeks of gestation, because it is during this time that the arms and legs develop.**



Malformations due to maternal ingestion of thalidomide (Schardein 1982 and Moore 1993).

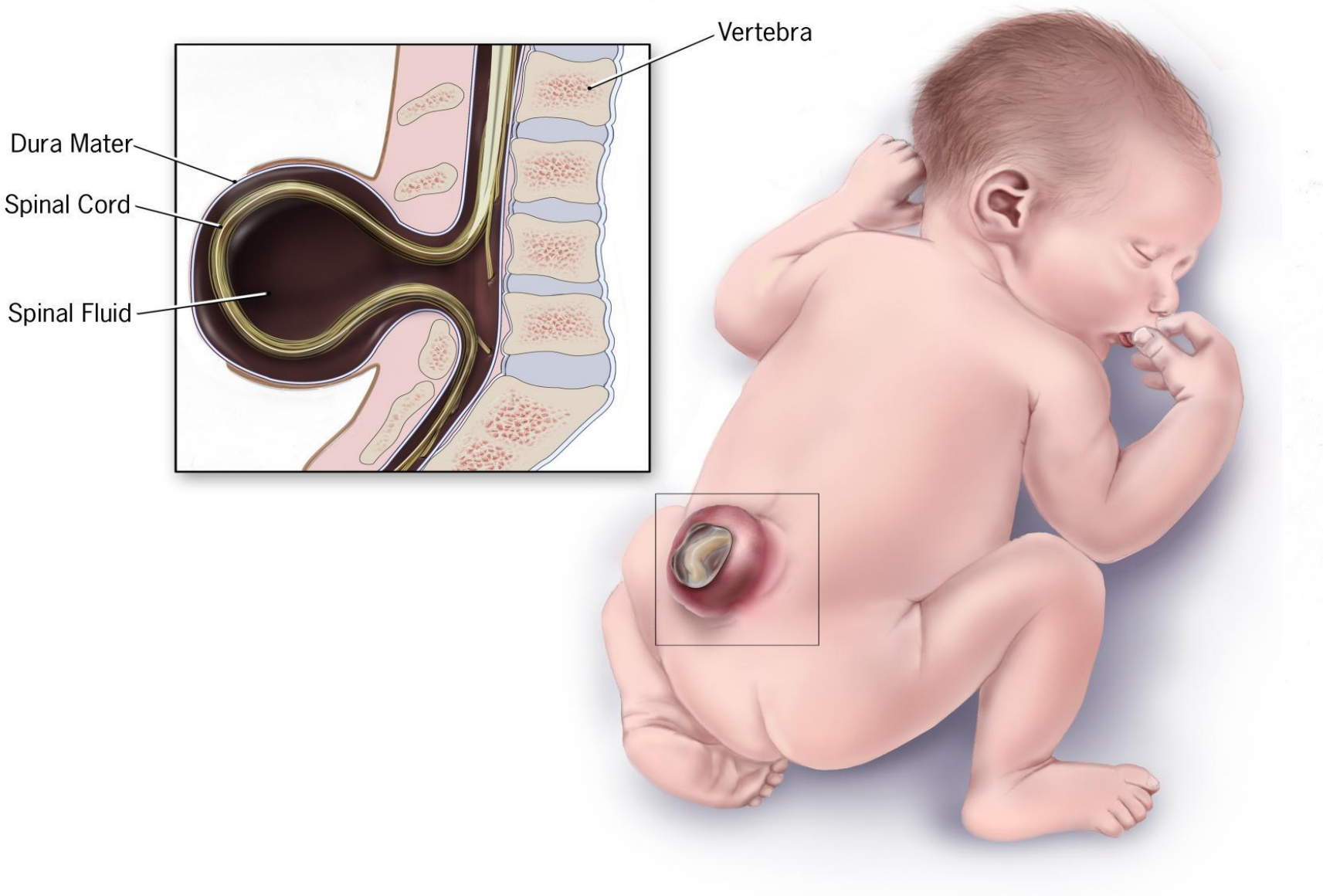
Teratogenic mechanisms

- **They are poorly understood and are probably multifactorial:**

1. **Folic acid deficiency, or use of folic acid antagonists, during pregnancy may produce neural tube defects (spina bifida).**

- **Folic acid supplementation during pregnancy reduces the incidence of neural tube defects.**
- **Rapidly proliferating tissues require DNA synthesis, which requires folate.**

Spina Bifida (Open Defect)



Teratogenic mechanisms

2. **Neural crest cells disruption:**

- **Neural crest cells are pluripoptent cell population that gives numerous structures.**
- **Disruption can be caused by endothelin receptor blockers (bosentan), folic acid antagonists, and retinoic acid.**

3. **Drugs may disrupt the normal processes of differentiation. Vitamin A analogs (isotretinoin, etretinate) are potent teratogens.**

Teratogenic mechanisms

4. **Endocrine disruptions (Sex hormones):**

- **Diethylstilbesterol increased the risk of vaginal adenocarcinoma in daughters, and hypospadius and cryptorchidism in sons of mothers taking it during pregnancy. (historic example)**

5. **Oxidative stress (reactive oxygen species) causes irreversible damage of DNA, proteins and lipids; leading to inactivation of many enzymes and cell death; and alteration of gene expression.**

Teratogenic mechanisms

6. Vascular disruption:

- **Refers to disruption in the circulation which include hypoperfusion, hyperperfusion, hypoxia and obstruction.**
- **Drugs may interfere with the passage of oxygen or nutrients through the placenta and have effects on the most rapidly metabolizing tissues of the fetus.**

Teratogenic mechanisms

7. **Chronic high consumption of ethanol during pregnancy, particularly during the first and second trimesters, may result in the "Fetal Alcohol Syndrome".**

- **In this syndrome the central nervous system, growth, and facial development may be affected.**

Fetal Alcohol Syndrome Symptoms

- **A small head, a smooth ridge between the upper lip and nose, small and wide-set eyes, a very thin upper lip, or other abnormal facial features, below average height and weight, hyperactivity, lack of focus, poor coordination, delayed development and problems in thinking, speech, movement, and social skills; poor judgment, problems seeing or hearing, learning disabilities, intellectual disability, heart problems, kidney defects and abnormalities, deformed limbs or fingers, mood swings.**


Small head
Low nasal bridge
Epicanthal folds
Small eye openings
Flat midface
Short nose
Thin upper lip
Smooth philtrum
Underdeveloped jaw
A.D.A.M.

Teratogenic mechanisms

8. Maternal Smoking During Pregnancy:

The Fetus may have the following anomalies:

a) **Cardiovascular defects.**

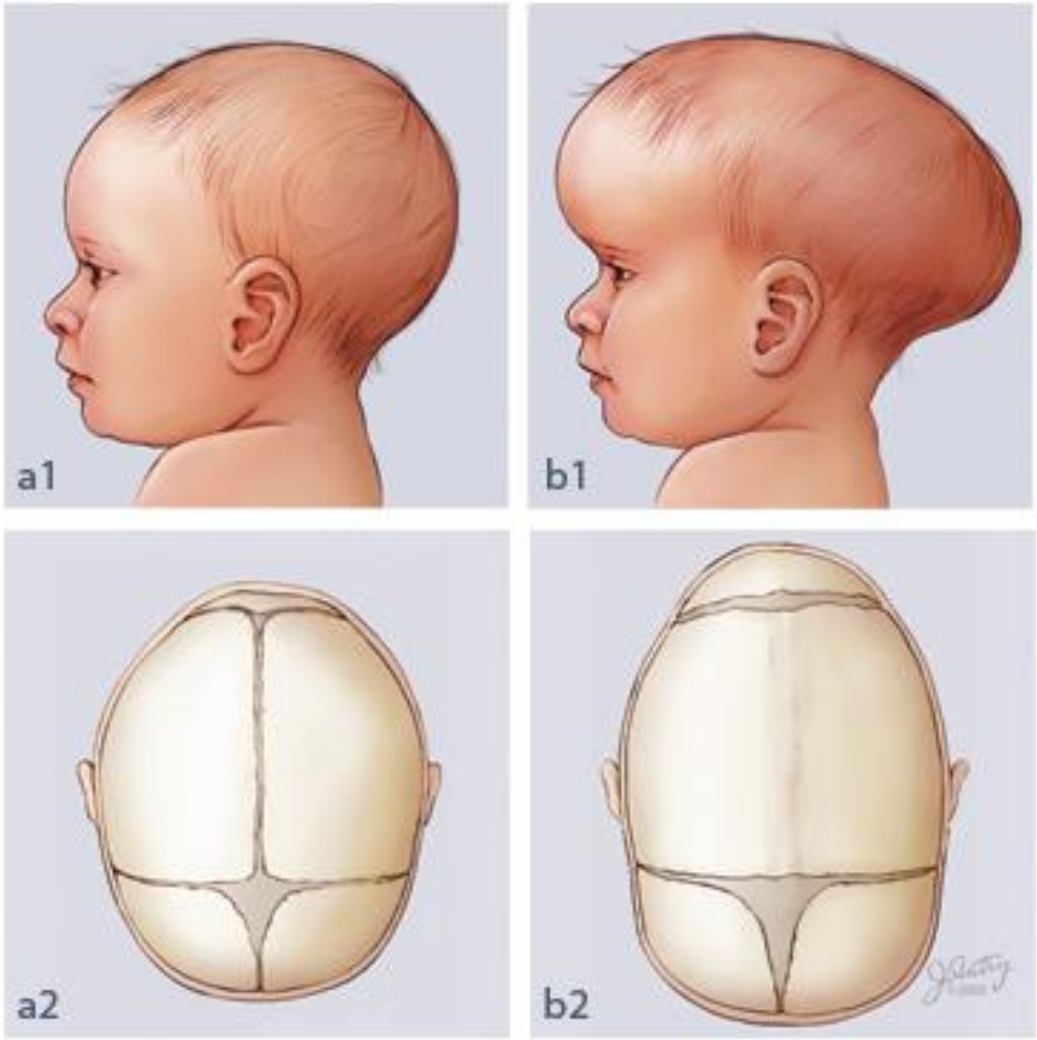
b) **Musculoskeletal defects and craniosynostosis.**

c) **Facial defects (face, nose, eyes or ears).**

d) **Defects of the gastrointestinal system.**

e) **Increased risk of early delivery – preterm.**

f) **Abortion.**


a1
b1
a2
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Teratogenic mechanisms

g) Abruptio placentae.
h) Slow fetal growth.
i) Learning disabilities.
j) Sudden infant death syndrome (SIDS).
k) Low birth-weight.
l) Mental retardation.
m) Cerebral palsy.

Defining a teratogen

To be considered teratogenic, a drug should:

1. **Result in a characteristic set of malformations, indicating selectivity for certain target organs.**
2. **Exert its effects at a particular stage of fetal development, during the limited time period of organogenesis of the target organs.**
3. **Show a dose-dependent incidence.**

Defining a teratogen

- **Drug effects on the fetus are NOT limited only to major malformations, but also include intrauterine growth retardation (cigarette smoking), miscarriage (alcohol), stillbirth (cigarette smoking), and neurocognitive delay (alcohol).**

Factors Affecting the Production of Congenital Malformations

A. The Dose of the Teratogen:

The effect is dose-dependent. Therefore, to prevent malformation give the mother the lowest effective dose for the shortest possible duration.

B. The developmental stage of the embryo:

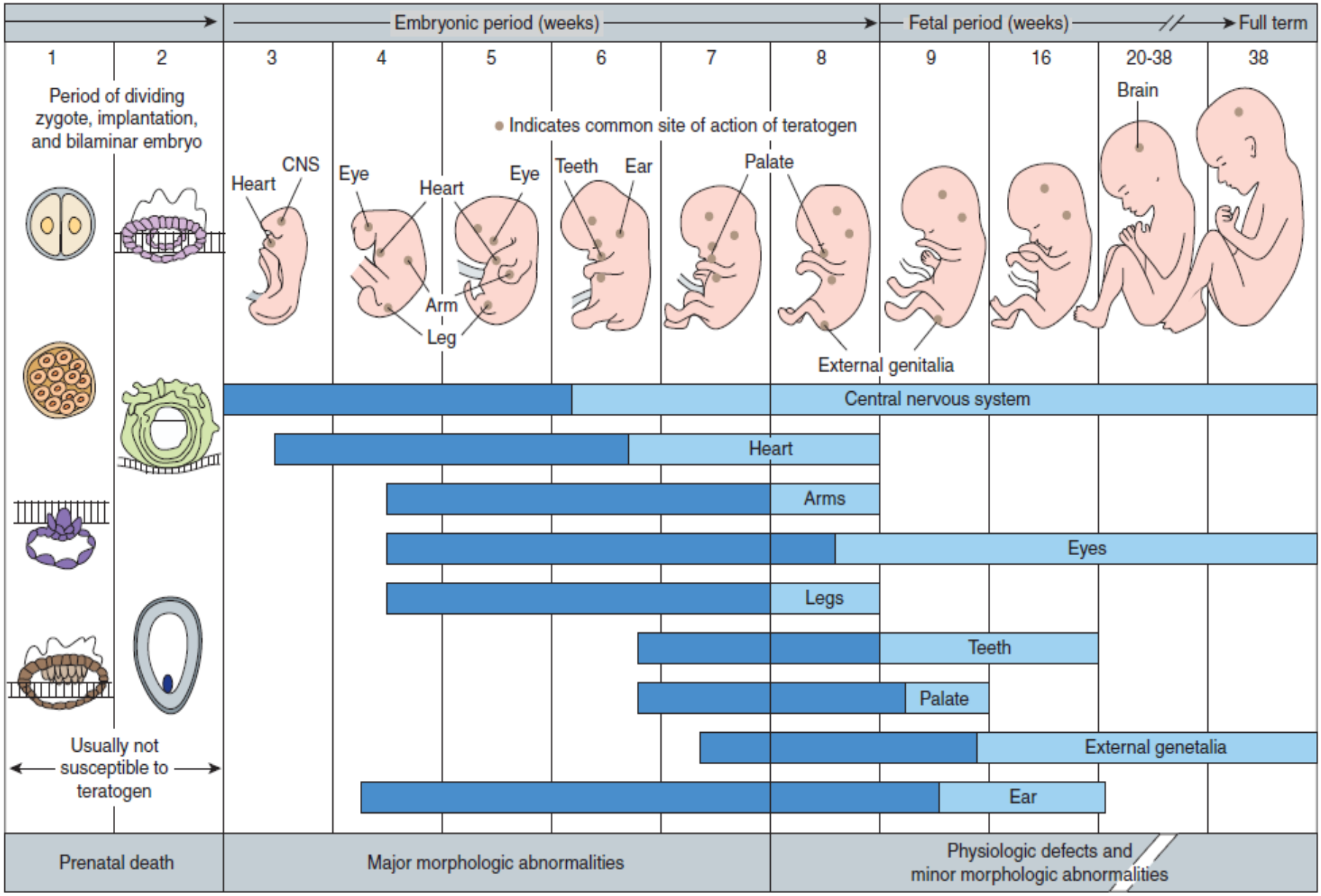

FIGURE 59–1 Schematic diagram of critical periods of human development. (Reproduced, with permission, from Moore KL: *The Developing Human: Clinically Oriented Embryology*, 4th ed. Saunders, 1988.)

Factors Affecting the Production of Congenital Malformations

1. **Blastogenesis:**

   (Time of fertilization - implantation, 1-8 days).

- **Exposure may kill blastocyst, NO evidence of production of congenital malformations.**
- **Up to 15th day after fertilization, cells are still totipotent and damaged cells can be replaced.**

Factors Affecting the Production of Congenital Malformations

2. **Embryogenesis:**

   Time of implantation - the end of 8th week (2nd – 8th week).

- **The vulnerability of the developing embryo to teratogens is greatest because this is the critical period for organogenesis.**
- **Exposure results in gross malformations or fetal death.**

Factors Affecting the Production of Congenital Malformations

3. **Fetogenesis:**

   (End of 8th week - end of pregnancy).

The most important events are:

a. **Differentiation of external genitalia.**
b. **Histogenesis of CNS.**

Results:

a. **Impairment of differentiation of external genitalia.**
b. **Behavioral changes or impairment of mental development.**

Factors Affecting the Production of Congenital Malformations

C. The Genetic Susceptibility of the Embryo:

- No teratogen produces congenital malformations in all fetuses

D. The physiological and Pathological status of the mother:

1) Age (< 18 and > 35 years → higher risk)
2) Nutritional status - malnutrition
3) Disease states - DM

Effect of Drugs Late in Pregnancy

- **No congenital malformations, but adverse effects are likely to occur.**

Examples:

1. **Salicylates may increase bleeding or delay labor → low birth weight.**
2. **ACEIs may produce irreversible fetal renal damage.**
3. **Opioids may produce dependence in the fetus.**

Effect of Drugs Very Near Delivery

- **No congenital malformations, but adverse effects are likely to occur.**

Examples:

1. **Thiopental may produce sedation and apnea in the newborn.**
2. **Opioids may produce apnea in the newborn.**

Counseling Women About Teratogenic Risk

1. Few drugs are known teratogens.
2. Evidence-based medicine should be practiced when talking about drug teratogenicity.
3. The risk of a neonatal abnormality in the absence of any known teratogenic exposure is about 3%.
4. Pregnancy outcomes are affected by maternal health status, life-style, and history prior to conception.

Counseling Women About Teratogenic Risk

5. **The maternal-fetal risks of the untreated condition (if a required medication is avoided) is high.**

- ***Recent studies have shown <u>serious morbidity</u> in women who discontinued selective serotonin reuptake inhibitor therapy for depression during pregnancy.***

Drug Associated with Congenital Malformations

- **Examples of drugs associated with congenital anomalies during organogenesis: methotrexate, cyclophosphamide, sex hormones (androgens, estrogens and progestins), lithium, retinoids, thalidomide, certain antiepileptic drugs, and coumarins.**
- **NSAIDs and tetracycline are likely to produce adverse effects during the second and third trimesters.**

Table 57.2 Some drugs reported to have adverse effects on human fetal development

Agent	Effect(s)	Teratogenicity[a]	See Chapter
Thalidomide	Phocomelia, heart defects, gut atresia, etc.	K	This chapter
Penicillamine	Loose skin etc.	K	26
Warfarin	Saddle nose; retarded growth; defects of limbs, eyes, central nervous system	K	24
Corticosteroids	Cleft palate and congenital cataract—rare	–	32
Androgens	Masculinisation in female	–	34
Oestrogens	Testicular atrophy in male	–	34
Stilbestrol	Vaginal adenosis in female fetus, also vaginal or cervical cancer	20+ years later	34
Phenytoin	Cleft lip/palate, microcephaly, mental retardation	K	44
Valproate	Neural tube defects (e.g. spina bifida)	K	44
Carbamazepine	Retardation of fetal head growth	S	44
Cytotoxic drugs (especially folate antagonists)	Hydrocephalus, cleft palate, neural tube defects, etc.	K	55
Aminoglycosides	Deafness	–	50
Tetracycline	Staining of bones and teeth, thin tooth enamel, impaired bone growth	S	50
Ethanol	Fetal alcohol syndrome	K	48
Retinoids	Hydrocephalus etc.	K	56
Angiotensin-converting enzyme inhibitors	Oligohydramnios, renal failure	K	22

[a]K, known teratogen (in experimental animals and/or humans); S, suspected teratogen (in experimental animals and/or humans).
Adapted from Juchau 1989 Annu Rev Pharmacol Toxicol 29: 165.

Fetal Hydantoin syndrome

Areas affected	Clinical features
Craniofacial abnormalities	Cleft lip, cleft palate, a broad depressed nasal bridge, low-set abnormal ears, broad alveolar ridges, and long philtrum
Ocular defects	Ocular hypertelorism, strabismus, ptosis of the eyelids, and inner epicanthic folds
Limb abnormalities	Hypoplasia of distal phalanges with small nails, a digital thumb, and dislocation of hip
Growth abnormalities	Impaired psychomotor performance and physical growth retardation
Miscellaneous (less frequent)	Nuchal webbing, a low hairline, rib and sternal anomalies, umbilical and inguinal hernias, cardiovascular anomalies, positional limb deformities, and gastrointestinal abnormalities

FDA Pregnancy Categories

Category A

Adequate and well-controlled studies have failed to demonstrate a risk to the fetus in the first trimester of pregnancy (and there is no evidence of risk in later trimesters).

Category B

Animal reproduction studies have failed to demonstrate a risk to the fetus and there are NO adequate and well-controlled studies in pregnant women.

Category C

Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.

FDA Pregnancy Categories

Category D

There is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.

Category X

Studies in animals or humans have demonstrated fetal abnormalities and/or there is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience, and the risks involved in use of the drug in pregnant women clearly outweigh potential benefits.

Meaning of FDA Pregnancy Categories of Drugs

1. **Category A: No evidence of fetal risk and is safe to use during in pregnancy.**
2. **Category B: Relatively safe.**
3. **Category C: Information about fetal risk is not available but risk can NOT be ruled out.**
4. **Category D: Positive evidence of fetal risk.**
5. **Category X: Definite fetal risk and the drug is contraindicated during pregnancy.**

Principles that Guide Drug Selection During Pregnancy

1. Effective old drugs are preferable to new alternatives.
2. Use the lowest effective dose for the shortest possible duration.
3. Discourage pregnant ladies from taking over-the-counter medications, supplements or herbs by themselves.
4. No drug is absolutely safe during pregnancy and at high doses categories can change.

Drug Selection During Pregnancy

Strategies to optimize the health of the mother while minimizing the risk to the fetus:

1. **Identification of the pattern of medication use before conception.**
2. **Eliminating nonessential medications.**
3. **Discouraging self medication.**
4. **Minimizing exposure to medications known to be harmful.**
5. **Adjusting medication dosing.**

Therapeutic Considerations in Pediatric Patients

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Therapeutic Considerations in Pediatric Patients

- **Children are NOT "little adults".**
- **There are variations among pediatric age groups in:**

a. **absorption of drugs from the gastrointestinal tract, intramuscular injection sites, and skin, especially in premature infants.**
b. **the rate and extent of organ function development.**
c. **distribution, metabolism, and elimination of drugs.**

Therapeutic Considerations in Pediatric Patients

- **The pediatric drug-use process is complex and error prone because of the multiple steps required in calculating, verifying, preparing, and administering doses.**

Therapeutic Considerations in Pediatric Patients

Pediatric patients are defined as those younger than 18 (or 16) years:

1. **Premature newborn: infants born before 37 weeks of gestational age.**
2. **Neonates are those between 1 day-1 month of age**
3. **Infants are those between 1 month - 1 year.**
4. **Children are those between 1 - 11 years of age.**
5. **Adolescents are those between 12 - 16 years of age.**

Therapeutic Considerations in Pediatric Patients

- **Only ~ ¼th of marketed drugs have indications specific for use in pediatric age groups.**
- **Data on the pharmacokinetics, pharmacodynamics, efficacy, and safety of drugs in infants and children are scarce.**
- **This has led to disasters in this population, such as gray baby syndrome from chloramphenicol, phocomelia from thalidomide, and kernicterus from sulfonamide therapy.**

Therapeutic Considerations in Pediatric Patients

- Identifying an optimal dosage is a real concern.
- **Dosage regimens can NOT be extrapolated accurately from adult dose, based simply on body weight or surface area of a pediatric patient.**
- **Bioavailability, pharmacokinetics, pharmacodynamics, efficacy, and safety information which differ markedly between pediatric and adult patients, do as well differ among pediatric patients themselves, because of differences in age, organ function, and disease state.**

Therapeutic Considerations in Pediatric Patients

- **Many drugs prescribed widely for neonates, infants, and children are NOT available in suitable dosage forms.**
- **Dilution or reformulation of dosage forms intended for adult patients raises questions about the bioavailability, stability, and compatibility of these drugs.**
- **Adherence to pharmacotherapy in pediatric patients is a special challenge.**

Therapeutic Considerations in Pediatric Patients

- **The need for additional therapeutic research in pediatric patients requires ethical justification.**
- **"Investigators proposing studies", and "institutional review committees" approving human studies must assess if the risk-to-benefit ratio of each study is fair to children who are NOT in a position to voluntarily accept or reject the participation in the research.**

Drug Absorption In Pediatric Groups

Gastrointestinal Tract:

- **Factors affecting the absorption of drugs from the GIT are pH-dependent passive diffusion, and gastric emptying time.**
- **Both processes are different in premature infants compared with older children and adults.**
- **In a full-term infant, gastric pH ranges from 6-8 at birth, and declines to 1-3 within 24 hours.**
- **In contrast, gastric pH remains elevated in premature infants because of immature acid secretion process.**

Drug Absorption In Pediatric Groups

- **In premature infants, higher serum concentrations of acid-labile drugs (penicillin, ampicillin, and nafcillin), and lower serum concentrations of a weak acids (phenobarbital) can be explained by higher gastric pH.**
- **The processes of both passive and active transport may NOT be fully developed before ~ 4 months of age.**

Drug Absorption In Pediatric Groups

- **The development and expression of the efflux transporter P-glycoprotein, and the intestinal drug-metabolizing enzymes (CYP3A) and their impact on drug bioavailability in infants and children, is NOT studied very well.**
- **Gastric emptying is slow in premature infants.**
- **Thus, drugs with limited absorption in adults may be absorbed efficiently in premature infants because of prolonged contact time with gastrointestinal mucosa.**

Drug Absorption In Pediatric Groups

Intramuscular Sites:

- **Differences in relative muscle mass, poor perfusion to various muscles, peripheral vasomotor instability, and insufficient muscular contractions in premature infants compared with older children and adults can influence drug absorption from the intramuscular site.**
- **The net effect of these factors on drug absorption is difficult to predict.**

Drug Absorption In Pediatric Groups

- **Phenobarbital absorption is rapid, whereas that of diazepam may be delayed.**
- **Thus, intramuscular injection is NOT used in neonates, except in emergencies or when an IV site is inaccessible.**

Drug Absorption In Pediatric Groups

Skin:

- **Percutaneous absorption may be increased in newborns because of an under-developed stratum corneum and increased skin hydration.**
- **The relative bioavailability of topically applied drugs, including corticosteroids, may be higher in infants and young children than in adults.**

Drug Absorption In Pediatric Groups

- **The increased exposure can produce toxic effects after topical use of hexachlorophene soaps and powders, salicylic acid ointment, and rubbing alcohol.**
- **A transdermal patch formulation of methylphenidate can be used in children 6-12 years of age for treatment of attention-deficit/-hyperactivity disorder (ADHD).**

Drug Distribution In Pediatric Groups

Drug distribution is determined by:

a. **The physicochemical properties of the drug itself (pka, molecular weight, and partition coefficient).**
b. **The physiologic factors specific to the patient (extracellular and total body water, plasma protein binding of the drug, and pathologic conditions).**

- **These physiologic functions often vary in different pediatric patient populations.**

Drug Distribution In Pediatric Groups

- **Total body water is 94% in fetuses, 85% in premature infants, 78% in full-term infants, and 60% in adults.**
- **Extracellular fluid volume may account for 50% of body weight in premature infants, 35% in 4-6 month-old infants, 25% in 1-year-old children, and 19% in adults.**
- **This is reflected on the volume of distribution of gentamicin of 0.48 L/kg in neonates and 0.20 L/kg in adults (as an example of water-soluble drug).**

Drug Distribution In Pediatric Groups

- **Binding of drugs to plasma proteins is decreased in newborn infants because of: decreased plasma protein concentration, lower binding capacity of protein, decreased affinity of proteins for drug binding, and competition for certain binding sites by endogenous compounds such as bilirubin.**
- **This affects free concentration of highly protein bound drugs (phenobarbital, salicylates, and phenytoin, warfarin ..).**

Drug Distribution In Pediatric Groups

- **The decrease in plasma protein binding of drugs can increase their apparent volumes of distribution, leading to the need for higher loading doses to achieve a therapeutic serum concentration (phenobarbital and phenytoin).**
- **Pharmacologic and toxic effects are related directly to the concentration of free drug in the body.**

Drug Distribution In Pediatric Groups

- **Increased mortality from the development of kernicterus secondary to displacement of bilirubin from albumin and other serum proteins by sulfonamides in neonates is well documented.**

Drug Distribution In Pediatric Groups

- The amount of body fat is substantially lower in neonates than in adults, which may affect drug therapy.
- Certain highly lipid-soluble drugs are distributed less widely in infants than in adults.
- The apparent volume of distribution of diazepam (fat-soluble) ranges from 1.4-1.8 L/kg in neonates and from 2.2 to 2.6 L/kg in adults.

Drug Metabolism In Pediatric Groups

- **Drug metabolism is substantially slower in infants than in older children and adults.**
- **There are differences in the maturation of various pathways of metabolism in infants.**
- **The sulfation pathway is well developed, but the glucuronidation pathway is undeveloped in infants.**

Drug Metabolism In Pediatric Groups

- **Acetaminophen metabolism by glucuronidation is impaired in infants compared with adults, but it is partly compensated for by the sulfation pathway.**
- **Chloramphenicol-induced gray baby syndrome in newborn infants is caused by decreased metabolism by glucuronosyltransferases to the inactive glucuronide metabolite.**
- **The full development of glucuronosyltransferases may take several months to 1 year after birth.**

Drug Metabolism In Pediatric Groups

- **Metabolism of drugs by oxidation is impaired in newborn infants (theophylline, phenobarbital, and phenytoin)**
- **CYP2C9 (phenobarbital and phenytoin) surpasses adult values by 2 weeks of age.**
- **CYP1A2 (theophylline) is NOT fully developed for several months.**
- **Theophylline clearance in children 1 to 9 years of age exceeds that in infants and adults.**

Drug Metabolism In Pediatric Groups

- **Premature infants receiving theophylline for treatment of apnea, metabolise it to caffeine, in contrast to older children and adults.**
- **Because of decreased metabolism, daily doses of drugs such as theophylline, phenobarbital, phenytoin, and diazepam should be decreased in premature infants.**

Drug Metabolism In Pediatric Groups

- **6-Mercaptopurine (6-MP), a drug commonly used in pediatric leukemias, undergoes metabolism by thiopurine S-methyltransferase (TPMT).**
- **There is an inherited deficiency of TPMT in 6-11% of patients.**
- **Children homozygous for the variant alleles require 6-MP dose reduction of ~ 90%, while heterozygotic children need a dose reduction of approximately 50% compared to patients with NO TPMT deficiency.**

Drug Excretion In Pediatric Groups

- **Drugs and their metabolites may be eliminated by the kidney.**
- **The glomerular filtration rate (GFR) may be as low as 0.6-0.8 mL/min/1.73 m^2 in preterm infants and approximately 2-4 mL/min/1.73 m^2 in term infants.**
- **The processes of glomerular filtration, tubular secretion, and tubular reabsorption determine the efficiency of renal excretion.**

Drug Excretion In Pediatric Groups

- **These processes may NOT develop fully for several weeks to 1 year after birth.**
- **Premature infants require a lower daily dose of drugs eliminated by the kidney during the first week of life.**
- **The dosage requirement then increases with age.**

Drug Efficacy And Toxicity In Pediatric Groups

- **Factors related to drug efficacy and toxicity should be considered in planning pediatric pharmacotherapy.**

1. **The maintenance dose of digoxin is higher in infants than in adults, because of a lower binding affinity of digoxin to its receptors in the myocardium.**
2. **Insulin requirements are highest during adolescence because of the individual's rapid growth.**

Drug Efficacy And Toxicity In Pediatric Groups

3. **Promethazine is contraindicated in children younger than 2 years because of the risk of severe respiratory depression.**
4. **Codeine toxicity and death have been reported after tonsillectomy and adenoidectomy in children who were ultrarapid metabolizers (Codeine is metabolized to morphine) and should NOT be used in these patients.**

Drug Efficacy And Toxicity In Pediatric Groups

5. **Propylene glycol, which is added to many injectable drugs (phenytoin, phenobarbital, digoxin, lorazepam, vitamin D, hydralazine, acetaminophen, diphenhydramine, furosemide, ibuprofen, and prednisone) to increase their stability, can cause hyperosmolality in infants.**

Drug Efficacy And Toxicity In Pediatric Groups

6. **Benzyl alcohol should not be used as preservative in pediatric formulation because it has been associated with severe morbidity and mortality in premature infants (metabolic acidosis, seizures, neurologic deterioration, gasping respirations, hepatic and renal abnormalities, cardiovascular collapse).**

Drug Efficacy And Toxicity In Pediatric Groups

7. **Safety of excipients have NOT been determined for infants and children.**
8. **Antihistamines, decongestants, antitussives, and expectorants used for common cold should NOT be used in children younger than 4 years of age because of lack of evidence for efficacy and safety.**

Drug Efficacy And Toxicity In Pediatric Groups

9. **Tetracyclines are contraindicated for use in pregnant women, nursing mothers, and children younger than 8 years because they can cause dental staining and defects in enamelization of deciduous and permanent teeth, as well as a decrease in bone growth.**

Drug Efficacy And Toxicity In Pediatric Groups

10. **Fluoroquinolones (ciprofloxacin) are generally NOT recommended for pediatric patients or pregnant women because the may affect the development of cartilage of weight-bearing joints, in addition to, arthropathy, tendonitis and tendon rupture in certain patients.**

Factors Affecting Pediatric Therapy

Hepatic Disease:

- **Studies on the influence of hepatic disease on dosage requirements have NOT been performed in pediatric patients.**
- **Routine hepatic function tests (serum aspartate aminotransferase, serum alanine aminotransferase, alkaline phosphatase, and bilirubin levels) may NOT correlate with drug pharmacokinetics.**

Factors Affecting Pediatric Therapy

- **Because of a lack of specific data on dosage adjustment in hepatic disease, drug therapy should be monitored closely in pediatric patients to avoid potential toxicity from excessive doses, particularly for drugs with narrow therapeutic indices.**

Factors Affecting Pediatric Therapy

Renal Disease:

- **Renal failure decreases the dosage requirement of drugs eliminated by the kidneys.**
- **Dosage adjustments in pediatric patients are based largely on data obtained in adults.**
- **For many important drugs, such as aminoglycoside antibiotics, renal clearance is directly proportional to the GFR, as measured by creatinine clearance.**

Factors Affecting Pediatric Therapy

- **GFR can be estimated using the Schwartz formula, which takes into account serum creatinine concentration and the patient's height, gender, and age:**

  $$GFR = K \times L/S_{Cr}$$

  where GFR is expressed in mL/min/1.73 m^2 of BSA, K = age-specific constant of proportionality, L = child's length in centimeters, and S_{Cr} = serum creatinine concentration in mg/dL.

- **Schwartz formula over-estimates GFR.**

Factors Affecting Pediatric Therapy

Age	*k*
<1 year of age, low-birth-weight infant	0.33
<1 year of age, full-term infant	0.45
2-12 year-old child	0.55
13-21 year-old female	0.55
13-21 year-old male	0.7

Factors Affecting Pediatric Therapy

- **The formula may NOT provide an accurate estimation of GFR in patients with rapidly changing serum creatinine concentrations in:**

a. **critical care setting**
b. **infants younger than 1 week**
c. **patients with obesity, malnutrition, or muscle wasting.**

- ***Factors that interfere with serum creatinine measurement also may cause errors in estimation of GFR.***

Factors Affecting Pediatric Therapy

- **Serum drug concentrations should be monitored for drugs with narrow therapeutic index and eliminated largely by the kidneys (vancomycin and aminoglycosides, ..) to optimize therapy in pediatric patients with renal dysfunction.**
- **For drugs with wide therapeutic ranges (penicillins and cephalosporins), dosage adjustment may be necessary only in patients with moderate to severe renal failure.**

Factors Affecting Pediatric Therapy

Cystic Fibrosis:

- **Increased doses of certain drugs (gentamicin, tobramycin, netilmicin, amikacin, dicloxacillin, cloxacillin, azlocillin, piperacillin, and theophylline) are required because of higher clearance values (cause unknown).**
- **The apparent volume of distribution of certain drugs also may be altered in cystic fibrosis.**

Factors Affecting Pediatric Therapy

Obesity:

- **Children and adolescents are classified as being overweight or obese according to body mass index (BMI) percentile:**

a. **Overweight children: BMI percentile > 85th - <95th.**

b. **Obese children: BMI percentile of > the 95th percentile.**

Factors Affecting Pediatric Therapy

- **Like adults, obese children are at risk for metabolic complications and the development of co-morbid conditions, including high blood pressure, high cholesterol (low HDL-cholesterol and high LDL-cholesterol), type 2 diabetes mellitus, nonalcoholic fatty liver disease, polycystic ovary disorder, cholecystitis, gastroesophageal reflux disease, and obstructive sleep apnea.**

Factors Affecting Pediatric Therapy

- **Obesity can impair the antileukemia efficacy of first-line chemotherapeutic agents and accelerate leukemia progression:**

1. **Adipocytes attract acute lymphoblastic leukemia (ALL) cells decreasing their exposure to anticancer drugs.**
2. **Adipocytes secrete asparagine, glutamine, and fatty acids that contribute to the survival of leukemia cells.**

- **High rates of life-threatening or fatal complications to chemotherapy have been reported with obese children and adolescents.**

Factors Affecting Pediatric Therapy

- **Obese children have a higher volume of distribution (V_D) for lipophilic drugs, and a lower V_D for hydrophilic medications compared with normal-weight children.**
- **Depending on drug distribution (V_D), dosing in children may be according to "actual body weight" or "ideal body weight", or by using a correction factor for body weight.**

Factors Affecting Pediatric Therapy

- **Correction factors are 0.3 for β-lactams, 0.45 for ciprofloxacin, and 0.4 for aminoglycosides, using the following formula:**

  [(Actual body weight - Ideal body weight) x Correction factor] + [Ideal body weight]

Factors Affecting Pediatric Therapy

- **Vancomycin distributes into total body water and other tissues and is eliminated primarily by glomerular filtration.**
- **Vancomycin is empirically dosed using actual body weight in overweight and obese children.**
- **Every-8-hour dosing is used initially; the frequency can be increased to every-6-hour dosing for complicated infections using serum concentration monitoring to individualize the dose.**

Pediatric Dosage Forms & Compliance

- Many drugs prepared for children are in the form of elixirs or suspensions.
- Elixirs are alcoholic solutions in which the drug molecules are dissolved and evenly distributed.
- No shaking is required.
- Unless some of the vehicle has evaporated, the first dose from the bottle and the last dose should contain equivalent amounts of drug.

Pediatric Dosage Forms & Compliance

- **Suspensions contain un-dissolved particles of drug that must be distributed throughout the vehicle by shaking.**
- **If shaking is NOT thorough each time a dose is given, the initial doses from the bottle may contain less drug than the last doses.**
- **This results in less than the expected plasma concentration or effect of the drug early in the course of therapy.**
- **Toxicity may occur late in the course of therapy.**

Pediatric Dosage Forms & Compliance

- **It is essential that the prescriber provides proper instructions to patient or parents on the use of dosage form.**
- **Adherence to therapy may be more difficult to achieve in pediatric practice, since it involves NOT only the parent's, but also practical matters such as measuring errors, spilling, and spitting out.**

Pediatric Dosage Forms & Compliance

- **The measured volume of “teaspoons” ranges from 2.5 to 7.8 mL.**
- **The parents should use a calibrated spoon or syringe, to improve the accuracy of dose measurements and simplify administration of drugs to children.**
- **Parents should be told what to do if the child has spelled part of the dose.**

Pediatric Dosage Forms & Compliance

- **The parents must be told what to do if the infant is sleeping at the scheduled time of the dose.**
- **Parents should have an explanation why an antibiotic use should continue for 10-14 days, even when the child improves after 4-5 days.**
- **Practical and convenient dosage forms and dosing schedules should be chosen to the extent possible.**
- **Adherence is better with easy dosing schedules.**

Pediatric Dosage Forms & Compliance

- **Depending on their ability to comprehend, children should be given some responsibility for their own health care and for taking medications.**
- **Instructions should utilize appropriate terms understandable by both the child and the parents.**
- **Possible adverse effects and drug interactions with over-the-counter medicines or foods should be discussed.**

Pediatric Dosage Forms & Compliance

- **Because many pediatric doses are calculated using body weight, major dosing errors may result from incorrect calculations.**
- **Tenfold errors due to incorrect placement of the decimal point have been described.**
- **Thus, avoid writing the dose as .1 mL because this can be mistaken by 1 mL, a 10-fold error. You should write 0.1 mL**
- **Avoid writhing a dose as 1.0 mL since this can be mistaken by 10 mL, again a 10-fold error. You should write 1 mL**

Pediatric Drug Dosage

- **For the majority of drugs, there are NO reliable pediatric dose information, because drugs are generally NOT evaluated in pediatric patients.**
- **Drugs approved for use in children do have recommended pediatric doses, stated as mg/Kg.**

Pediatric Drug Dosage

- **In the absence of pediatric dose recommendations, an approximation can be made by several methods based on age, weight, or surface area.**
- **These rules are NOT precise and should NOT be used if a pediatric dose is provided (based on studies in pediatric patients).**
- **When pediatric doses are calculated by any method, they should never exceed the adult dose.**

Pediatric Drug Dosage

1. **Surface Area, Age, & Weight:**

- **Calculations of dosage based on age or weight are conservative and tend to underestimate the required dose.**

a) **Doses based on surface area are more likely to be adequate.**

Child dose=

$$\frac{\text{Body surface area in } m^2 \text{ of child} \times \text{adult dose}}{1.73}$$

TABLE 59–6 Determination of drug dosage from surface area.[1]

Weight		Approximate Age	Surface Area (m^2)	Percent of Adult Dose
(kg)	(lb)			
3	6.6	Newborn	0.2	12
6	13.2	3 months	0.3	18
10	22	1 year	0.45	28
20	44	5.5 years	0.8	48
30	66	9 years	1	60
40	88	12 years	1.3	78
50	110	14 years	1.5	90
60	132	Adult	1.7	102
70	154	Adult	1.76	103

[1]For example, if adult dose is 1 mg/kg, dose for 3-month-old infant would be 0.18 mg/kg or 1.1 mg total.

Pediatric Drug Dosage

- **Age (Young's rule):**

$$Dose = \text{Adult dose} \times \frac{\text{Age (years)}}{\text{Age} + 12}$$

- **Weight (somewhat more precise is Clark's rule):**

$$Dose = \text{Adult dose} \times \frac{\text{Weight (kg)}}{70}$$

- Many times you do not need to use these equations when dosing recommendations are available.

Drug Use in the Elderly

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Therapeutic Considerations in the Elderly

- **Elderly patients are those 65 years of age and older.**
- **The health characteristics of those 65-74 years of age are different from those who are 85 years of age and older.**
- **Institutionalized individuals are also different from those living in the community.**
- **Age-related changes in physiology can affect the pharmacokinetics and pharmacodynamics of drugs.**

Therapeutic Considerations in the Elderly

- **Drug-related problems in older adults are common and cause significant morbidity.**
- **Common medical conditions in the elderly include: hypertension, diabetes mellitus, osteoporosis, bronchial asthma, COPD, cancer, arthritis, heart diseases, Alzheimer's disease and cognitive dysfunction, and stroke.**
- **The most common sensory impairments are: difficulties in hearing and vision.**
- **The elderly are also prone to falls.**

Human Aging & Changes in Drug Pharmacokinetics and Pharmacodynamics

Clinical manifestations of normal aging include:

1. **Changes in biochemical makeup of tissues.**
2. **Reduced functional capacity of body systems.**
3. **Reduced ability to adapt to physiological stress.**
4. **Increased vulnerability to disease.**
5. **Frailty (weakness, fatigue, weight loss and functional decline). (ضعف و هشاشة)**

- **Individuals experience aging at different rates.**

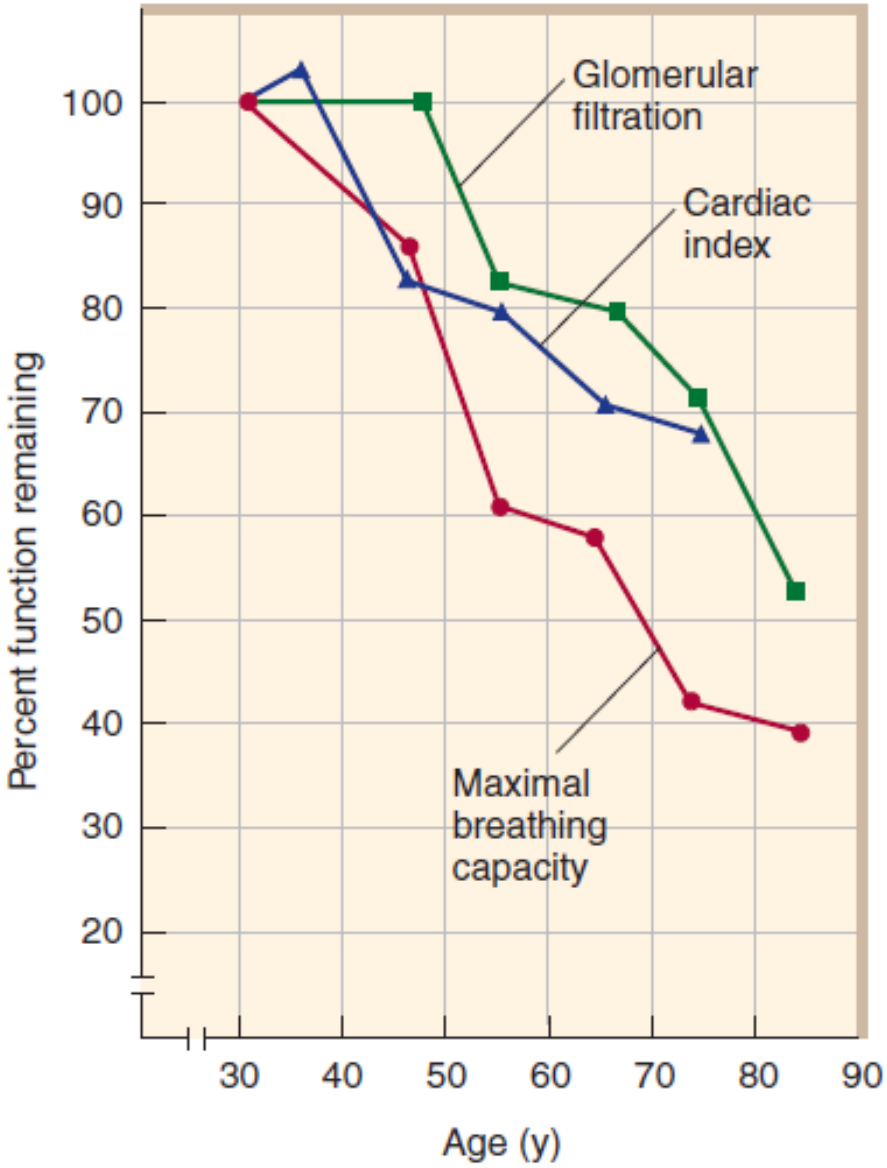

FIGURE 60–1 Effect of age on some physiologic functions.

(Modified and reproduced, with permission, from Kohn RR: *Principles of Mammalian Aging*. Prentice-Hall, 1978.)

TABLE 60–1 Some changes related to aging that affect pharmacokinetics of drugs.

Variable	Young Adults (20–30 years)	Older Adults (60–80 years)
Body water (% of body weight)	61	53
Lean body mass (% of body weight)	19	12
Body fat (% of body weight)	26–33 (women)	38–45
	18–20 (men)	36–38
Serum albumin (g/dL)	4.7	3.8
Kidney weight (% of young adult)	(100)	80
Hepatic blood flow (% of young adult)	(100)	55–60

Common Physiological Changes Associated with Aging

These changes include:

a) **Reduced functional reserve capacity.**

b) **Reduced ability to maintain homeostasis, making them susceptible to de-compensation in stressful situations.**

Examples of such impaired homeostatic mechanisms:

1) **Postural or gait stability**
2) **Orthostatic blood pressure responses**
3) **Thermoregulation**
4) **Cognitive reserve**
5) **Bowel or bladder function.**

Age-Related Altered Drug Pharmacokinetics

Absorption:

1. **Absorption of drugs may be affected by age-related changes in GIT physiology, drug-food interactions, concurrent medication, and co-morbidities affecting GI function.**

- **The bioavailability of drugs absorbed by passive diffusion may not be affected significantly.**
- **Drugs absorbed by active transport (vitamin B_{12}, calcium, iron, magnesium) may have impaired absorption.**

Age-Related Altered Drug Pharmacokinetics

2. First-pass effect is decreased, bioavailability and plasma concentration are increased for drugs such as propranolol and labetolol.
3. There is reduced bioavailability of some pro-drugs such as enalapril and codeine.
4. In atrophic gastritis, or in patients taking gastric acid-lowering agents, extent of absorption of some drugs may be reduced (ketoconazole, iron, digoxin, and atazanavir). These drugs require an acidic environment for absorption.

Age-Related Altered Drug Pharmacokinetics

Distribution:

Factors that influence drug distribution in the elderly:

1. **Altered plasma protein concentrations**
2. **Individual body composition (body fat and intracellular fluid content)**
3. **Decreased muscle and tissue mass**
4. **Reduced blood flow to tissues and organs.**
5. **Active uptake into tissues may also be influenced by ageing.**

Age-Related Altered Drug Pharmacokinetics

- **The volume of distribution of water-soluble drugs (ethanol, gentamicin, digoxin, and cimetidine) is reduced.**
- **Lipophilic drugs (benzodiazepines, metronidazole, and rifampin) exhibit an increased volume of distribution.**
- **Changes in the volume of distribution affect loading doses of drugs.**

Age-Related Altered Drug Pharmacokinetics

- **The brain of elderly patients may be exposed to higher concentrations of drugs and toxins because of age-related changes in the blood-brain-barrier.**

Age-Related Altered Drug Pharmacokinetics

Metabolism:

- **Hepatic metabolism of drugs depends on liver perfusion, activity and capacity of drug metabolizing enzymes, and protein binding.**
- **All of these factors are affected by the aging process.**

➢ **For drugs that have high intrinsic clearance (high hepatic extraction ratio), hepatic clearance depends on hepatic blood flow mainly (flow-limited metabolism).**

Age-Related Altered Drug Pharmacokinetics

- **Age-related decreases in hepatic blood flow (20-50%) can decrease significantly the metabolism of high extraction ratio drugs (propranolol, amitriptyline, diltiazem, lidocaine, metoptolol, morphine and verapamil).**

➢ **For drugs that have low intrinsic clearance (low hepatic extraction ratio), clearance depends on hepatic enzyme activity (capacity-limited metabolism).**

Age-Related Altered Drug Pharmacokinetics

- **Generally, liver size and its enzyme content are reduced in the elderly.**
- **Hepatic metabolism of warfarin, piroxicam and lorazepam is reduced with aging.**
- **Metabolism of phenytoin, ibuprofen, and naproxen is increased with aging.**
- **Metabolism of diazepam, temazepam, and valproic acid is NOT affected with aging.**

Age-Related Altered Drug Pharmacokinetics

- **Serum albumin concentration declines with age.**

✓ **For capacity-limited metabolism, the fraction of the drug unbound will increase for drugs with extensive protein binding, leading to increased total hepatic clearance (naproxen).**

- **Generally, phase II drug metabolism, in contrast to phase I, is preserved in the elderly.**
- **Frail older adults may experience reduced phase II drug metabolism as well.**

Age-Related Altered Drug Pharmacokinetics

Elimination:

- **Age-related reductions in GFR are well documented.**
- **Serum creatinine is a poor indicator of renal function in the elderly because creatinine is produced by muscles and there is reduced muscle mass in the elderly.**

Age-Related Altered Drug Pharmacokinetics

- **Cockcroft and Gault equation may be used to calculate creatinine clearance:**

$$\text{Creatinine clearance} = \frac{(140 - \text{Age})\,(\text{Actual body weight})}{72\,(\text{Serum creatinine concentration})}$$

Multiply the result by 0.85 for females.

➢**You should measure CL_{cr} accurately when you plan dose adjustment in patients with reduced renal function.**

Age-Related Altered Drug Pharmacokinetics

- **Dosing guidelines of drugs that are eliminated by the kidney are based on creatinine clearance.**

✓ **Some drugs should be avoided when CLcr < 30 mL/min: colchicine, co-trimoxazole, glyburide, nitrofurantoin, probenecid, spironolactone, triamterene.**

✓ **Some drugs need dose reduction in reduced renal function: acyclovir, amantadine, ciprofloxacin, gabapentin, ranitidine.**

Age-Related Altered Drug Pharmacodynamics

- **Changes in PDs are less understood than changes pharmacokinetics.**

Proposed changes leading to altered pharmacodynamics of drugs may include:

1. **Changes in drug concentration at the receptor.**
2. **Changes in receptor numbers.**
3. **Changes in receptor affinity.**
4. **Post-receptor changes.**
5. **Age-related changes in homeostatic mechanisms.**

Age-Related Altered Drug Pharmacodynamics

Older adults are more sensitive to the CNS effects of drugs:

1. **Changes in size and weight of brain.**
2. **Changes in the neurotransmitter systems.**
3. **Drugs penetrate CNS easier than in young adults.**

- **For example, in the elderly there is decreased levels of dopamine transporters, decreased number of dopaminergic neurons, and decreased density of dopamine receptors; leading to increased sensitivity to the adverse effects of antipsychotic drugs.**

Age-Related Altered Drug Pharmacodynamics

- There is increased sensitivity to benzodiazepines, opioids, general anesthetics antipsychotics, lithium and anticholinergic drugs.
- The elderly are more likely to develop orthostatic hypotension as an adverse effect of some drugs.

Age-Related Altered Drug Pharmacodynamics

There is also:

- **Increased hypotensive and bradycardic effect to calcium channel blockers.**
- **Reduced blood pressure response to β-blockers.**
- **Reduced effectiveness of diuretics.**
- **Increased risk of bleeding with warfarin.**

Drug-Related Problems in the Elderly

Include 3 important, potentially preventable, negative outcomes:

1. **Withdrawal effects.**
2. **Therapeutic failure.**
3. **Adverse drug reactions.**

Drug-Related Problems in the Elderly

Risk Factors:

1. **Polypharmacy including prescription and non-prescription drugs, herbal medicines, supplements and unnecessary drugs.**

- **Polypharmacy has been strongly associated with ADRs, risk of geriatric syndromes (falls, cognitive impairment), non-adherance, diminished functional status, and increased health care costs.**

Drug-Related Problems in the Elderly

2. **Inappropriate Prescribing, which includes:**

a. **Wrong dose and duration.**

b. **Duplication.**

c. **Drug interaction problem.**

d. **Prescription of drugs that should be avoided in the elderly. *********

3. **Underuse:**

- **Omission of drug therapy that is indicated in prevention or treatment of disease.**

Drug-Related Problems in the Elderly

4. Medication non-adherence:

Causes:

a. **Adverse effects.**
b. **Complex regimens.**
c. **Misunderstanding of information about prescribed medications.**
d. **Cost.**
e. **Dys-mobiliy (arthritis, ..).**
f. **Social factors (living alone).**
g. **Dementia.**

Assessing and Monitoring Drug Therapy

1. **Compare the patient's problem list with drug list:**

A drug may be considered unnecessary if:

a. **It does NOT have indication per the problem list.**
b. **Is NOT effective.**
c. **The risk of its use outweighs the benefits.**
d. **There is therapeutic duplication.**

Assessing and Monitoring Drug Therapy

2. **Determine if the patient is having a chronic condition but is NOT receiving an evidence-based medication to improve outcome.**
3. **Monitor efficacy and toxicity of drugs by clinical assessment and lab tests.**

- **Examples:**

Amiodarone	**hepatic function tests**
Antiepileptics	**Drug level**
ACEi &ARBs	**Serum K^+ level**

Assessing and Monitoring Drug Therapy

Antipsychotics	**Extrapyramidal ADRs**
Diuretics	**Serum K^+ level**
Hypoglycemics	**Glucose and glycated Hb**
Lithium	**Serum level**
Warfarin	**PT or INR**
etc..	

Assessing and Monitoring Drug Therapy

4. **Documenting problems and formulating a therapeutic Plan:**

- **A reasonable clinical outcome for a 40-year-old patient may NOT be reasonable for an 80-year-old patient.**
- **Take into account: remaining life expectancy, time until therapeutic benefit, treatment target, medication regimen complexity and goals of care, when deciding on prescribing rationale.**

Assessing and Monitoring Drug Therapy

5. Implement a team-based management approach and develop strategies to avoid prescribing errors.
6. Take measures to enhance adherence to medications:

a. Modify medication schedule to fit patient's life-style.

b. Prescribe generic agents to reduce cost.

Assessing and Monitoring Drug Therapy

c. Offer easy-to-open bottles.
d. Offer easy-to-swallow dosage forms.
e. Provide both written and oral drug information.
f. Involve caregivers stressing the importance of adherence.

Assessing and Monitoring Drug Therapy

- **Assess the presence of drug-disease interactions:**

  Anticholinergics: benign prostatic hyperplasia & dementia or cognitive impairment.

  Antipsychotics: history of falls & Parkinson's disease.

  Aspirin: peptic ulcer disease.

  Calcium Channel blockers: heart failure.

  Metoclopramide: Parkinson's disease.

  NSAIDs: peptic ulcer disease, heart failure, renal failure.

Table 2. 2015 American Geriatrics Society Beers Criteria for Potentially Inappropriate Medication Use in Older Adults

Organ System, Therapeutic Category, Drug(s)	Rationale	Recommendation	Quality of Evidence	Strength of Recommendation	Evidence
Anticholinergics					
First-generation antihistamines: Brompheniramine Carbinoxamine Chlorpheniramine Clemastine Cyproheptadine Dexbrompheniramine Dexchlorpheniramine Dimenhydrinate Diphenhydramine (oral) Doxylamine Hydroxyzine Meclizine Promethazine Triprolidine	Highly anticholinergic; clearance reduced with advanced age, and tolerance develops when used as hypnotic; risk of confusion, dry mouth, constipation, and other anticholinergic effects or toxicity Use of diphenhydramine in situations such as acute treatment of severe allergic reaction may be appropriate	Avoid	Moderate	Strong	2015 Criteria: Duran 2013 Fox 2014 Kalisch Ellet 2014 From previous criteria: Agostini 2001 Boustani 2007 Guaiana 2010 Han 2001 Rudolph 2008
Antiparkinsonian agents Benztropine (oral) Trihexyphenidyl	Not recommended for prevention of extrapyramidal symptoms with antipsychotics; more-effective agents available for treatment of Parkinson disease	Avoid	Moderate	Strong	Rudolph 2008
Antispasmodics: Atropine (excludes ophthalmic) Belladonna alkaloids Clidinium-	Highly anticholinergic, uncertain effectiveness	Avoid	Moderate	Strong	Lechevallier-Michel 2005 Rudolph 2008

American Geriatric Society Beers Criteria for Potentially inappropriate medication Use in Older Adults

1. **Anticholinergics + other drugs with anticholinergic activity such as antihistamines:**

- **Rationale: elimination reduced in older adults.**
- **Risk: confusion, dry mouth, constipation, urine retention.**
- **Quality of evidence: moderate.**
- **Strength of recommendation: strong.**

2. **Nitrofurantoin:**

- **Rationale: potential for pulmonary toxicity, hepatotoxicity, and peripheral neuropathy.**
- **Quality of evidence: low.**
- **Strength of recommendation: strong.**

3. **Peripheral and central α-blockers:**

- **Rationale: High risk of adverse effects, orthostatic hypotension, and CNS adverse effects.**
- **Quality of evidence: moderate - low.**
- **Strength of recommendation: strong.**

4. **Immediate-release nifedipine:**

- **Rationale: potential for hypotension and myocardial ischemia.**
- **Quality of evidence: high.**
- **Strength of recommendation: strong.**

5. **Amiodaraone:**

- **Rationale: High risk of many adverse effects.**
- **Quality of evidence: high.**
- **Strength of recommendation: strong.**

6. **Antidepressants:**

- **Rationale: highly anticholinergic, sedating, orthostatic hypotension and myocardial ischemia.**
- **Quality of evidence: high.**
- **Strength of recommendation: strong.**

7. **Antipsychotics:**

- **Rationale: increased risk of CVA, cognitive decline, dementia, and mortality.**
- **Quality of evidence: moderate.**
- **Strength of recommendation: strong.**

7. **Barbiturates & benzodiazepines:**

- **Rationale: highly rate of dependence, tolerance, sedation, cognitive impairment, delirium, falls, fractures.**
- **Quality of evidence: high - moderate.**
- **Strength of recommendation: strong.**

8. **Insulin sliding scale (refers to the progressive increase in the pre-meal or night-time insulin dose, based on pre-defined blood glucose ranges):**

- **Rationale: increased risk of hypoglycemia.**
- **Quality of evidence: moderate.**
- **Strength of recommendation: strong.**

9. **Long-acting sulfonylureas:**

- **Rationale: increased risk of hypoglycemia.**
- **Quality of evidence: high.**
- **Strength of recommendation: strong.**

10. **Metoclopramide:**

- **Rationale: increased risk of extrapyramidal adverse effects, dyskinesia.**
- **Quality of evidence: moderate.**
- **Strength of recommendation: strong.**

11. Proton pump inhibitors:

- **Rationale: risk of *Clostridium difficile* infection.**
- **Quality of evidence: high.**
- **Strength of recommendation: strong.**

12. Meperidine (pethidine):

- **Rationale: high risk of neurotoxicity, including delirium.**
- **Quality of evidence: moderate.**
- **Strength of recommendation: strong.**

13. NSAIDs:

- **Rationale: Increased risk of peptic ulcer disease, cardiovascular disease, renal failure.**
- **Quality of evidence: moderate.**
- **Strength of recommendation: strong.**

14. Central muscle relaxants (chlorzoxazone, cyclobenzaprine, orphenadrine):

- **Rationale: poorly tolerated because of anticholinergic effects, sedation, increased risk of falls and fractures.**
- **Quality of evidence: moderate.**
- **Strength of recommendation: strong.**

Drug Therapy in Patients with Chronic Kidney Disease (CKD)

Yacoub Irshaid, MD, PhD, ABCP

Drug Therapy in Patients with CKD

- **Individualization of a drug dosage regimen for a patient with reduced kidney function is based on:**

1. **The pharmacodynamics/pharmacokinetics of the drug.**
2. **Residual renal function.**
3. **The overall clinical condition of the patient.**

Drug Therapy in Patients with CKD

- **In addition to the decrease in renal clearance, non-renal clearance (gastrointestinal and hepatic drug metabolism) of several drugs is also reduced.**

GFR Category	GFR (mL/min/1.73 m^2)	Renal dysfunction
1	>90	Normal function
2	60–89	Mild
3a	45–59	Mild- to -moderate
3b	30–44	Moderate- to - severe
4	15–29	Severe
5	<15	Renal failure

Drug Therapy in Patients with CKD

- **Medications which are predominantly eliminated unchanged by the kidney may accumulate in CKD patients, leading to an increase the risk of adverse effects.**
- **If 30% or more of a drug is eliminated unchanged in the urine, it may require dosage adjustment in CKD patients, especially in those with stage 3 - 5 disease.**

Drug Therapy in Patients with CKD

- **Changes in protein binding, altered cytochrome P450 enzyme activity, and altered trans-cellular transport systems that are associated with CKD may affect serum and tissue drug concentrations and necessitate drug dosing adjustments.**

Drug Therapy in Patients with CKD

- **The dosage of many drugs must be altered to prevent toxicity, without compromising the achievement of the desired therapeutic outcome.**
- **Dangerous dosing errors in CKD patients still occur.**

Pharmacokinetic Changes In CKD

Drug Absorption:

- **The absorption and bioavailability of some drugs is highly variable in CKD patients.**
- **The mechanisms responsible are multifactorial and include; drug interactions, delayed gastric emptying, and reduced gastric acidity.**
- **Decreased gastrointestinal (GI) motility secondary to gastroparesis in patients with diabetes may delay the t_{max} (time to peak)and may also reduce the C_{max} (peak concentration).**

Pharmacokinetic Changes In CKD

- If a drug undergoes GI metabolism, the slower transit time allows for more GI metabolism and thus lower C_{max} of the parent drug.
- Urea retention in CKD patients results in a high influx of urea into the gut, which is converted to ammonia, leading to an increase in gastric pH.
- The increase in gastric pH may alter the dissolution or ionization properties of weakly basic drugs leading to changes in absorption.

Pharmacokinetic Changes In CKD

- **A reduction in gastric acidity, associated with the concomitant administration of antacids, H_2-receptor antagonists, proton pump inhibitors, and phosphate binders reduce the bioavailability of several antibiotics and digoxin.**
- **Antacids and multivitamin supplements may decrease the bioavailability of some drugs as a result of the formation of insoluble salts or metal ion chelates.**

Pharmacokinetic Changes In CKD

- **Edema of the GI tract, secondary to cirrhosis or congestive heart failure in CKD patients, can decrease the absorption of some drugs (reduce oral absorption of furosemide from 10 – 50%).**
- **The bioavailablity of only a few drugs (dextropropoxyphene, dihydrocodeine, felodipine, sertraline, and cyclosporine) increases in CKD patients.**
- **This is due to reduction in first-pass metabolism.**

Pharmacokinetic Changes In CKD

- **Drug interactions may independently alter bioavailability.**
- **Bioflavonoids in grapefruit juice inhibit CYP3A4 enzyme and noncompetitively inhibit the metabolism of drugs metabolized by this enzyme.**
- **This interaction can increase the bioavailability of cyclosporine by as much as 20%.**

Pharmacokinetic Changes In CKD

Distribution:

- **The V_D of many drugs may be increased in categories 3-5 CKD patients leading to a reduction in serum drug concentration.**
- **The increase in V_D may be due to: fluid overload secondary to excessive fluid administration or intake, or decreased plasma protein binding.**

Pharmacokinetic Changes In CKD

- **Decreased tissue binding of drugs in CKD patients may result in a reduction in V_D (digoxin and pindolol).**
- **Variability in fluid status is common in patients with severe CKD (category 4 & 5), especially those that are critically ill.**

Changes of Volume of Distribution of Selected Drugs in Patients with ESRD

Increased V_D	Decreased V_D
Aminoglycosides, Cephalosporins, Dicloxacillin, Erythromycin, Furosemide, Isoniazide, Naproxen, Phenytoin, Trimethoprim, Vancomycin…	B-blockers, Ciprofloxacin, Digoxin, Ethambutol, Methicillin…

Pharmacokinetic Changes In CKD

- **Many critically ill patients receive large volumes of IV fluids, and can subsequently develop edema, pleural effusions, or ascites.**
- **These, in addition to reduced water excretion in CKD, may lead to an increase the V_D of water-soluble drugs and decrease their serum concentration (aminoglycosides and cephalosporins V_D may be increased by up to 150%).**

Pharmacokinetic Changes In CKD

Effect of Altered Plasma Protein Binding:

- **Many drugs have altered protein binding in CKD patients.**
- **Protein binding of many acidic drugs is reduced (penicillins, cephalosporins, aminoglycosides, furosemide, and phenytoin) secondary to:**

Pharmacokinetic Changes In CKD

1. **Hypoalbuminemia.**
2. **Qualitative changes in the conformation of the protein binding site.**
3. **Competition for binding sites by other drugs, metabolites, and endogenous waste products than accumulate in renal dysfunction.**

Pharmacokinetic Changes In CKD

- **Protein binding of phenytoin (90% protein-bound, primarily to albumin) is significantly reduced secondary to decreased plasma phenytoin binding affinity for albumin, as well as low serum albumin, leading to an increase in the unbound concentration.**
- **These changes alter the relationship between total phenytoin concentration and desired or toxic effects.**

Pharmacokinetic Changes In CKD

- **The increase in unbound fraction, from 10% in normal renal function to 20% or more in category 5 CKD, results in increased hepatic clearance and decreased total concentrations.**
- **Thus, the therapeutic range based on total phenytoin concentration is shifted downward from 10-20 mg/L to values as low as 4-8 mg/L.**
- **However, the unbound concentration range remains the same for all patients (normal or CKD).**

Pharmacokinetic Changes In CKD

- **One can approximate the total phenytoin concentration that would be observed in category 5 CKD patients if they had normal plasma protein binding ($C_{\text{normal binding}}$).**
- **For albumin expressed in g/L the equation is:**

$$C_{\text{total normal binding}} = C_{\text{total reported}} / [(0.9)(0.48)\ (\text{albumin}/44)] + 0.1$$

Pharmacokinetic Changes In CKD

- **The principal binding protein for several basic drugs is α_1-acid glycoprotein, an acute-phase reactant protein, whose plasma concentrations are increased in CKD patients.**
- **As a result, the unbound fraction of some basic drugs (disopyramide) may be significantly decreased in CKD patients.**

Pharmacokinetic Changes In CKD

Effect of Altered Tissue Binding:

- Few drugs (pindolol, ethambutol, and digoxin) are affected.
- Tissue binding is reduced and the V_D of digoxin is decreased by 50% in patients with category 5 CKD, leading to elevated serum concentrations.
- In this case, the absolute amount of digoxin bound to the receptor is reduced.

Pharmacokinetic Changes In CKD

Elimination:

- **Elimination of a drug from the body is expressed as total systemic clearance (CL_T), which is defined as the sum of renal clearance (CL_R) and non-renal clearance CL_{NR}.**
- **Remember that total clearance does NOT only reflect drug elimination. It is also affected by drug distriburion ($CL_T = K.V_D$).**

Pharmacokinetic Changes In CKD

Non-renal Clearance:

- CL_{NR} refers to all routes of drug elimination, except renal excretion of unchanged drug.
- It includes hepatic and extrahepatic metabolism and transcellular transport pathways.
- It might be affected by renal disease.

Pharmacokinetic Changes In CKD

Accumulation of Metabolites:

- **Drugs that are eliminated by glomerular filtration, and given to category 4 & 5 CKD patients may have significant accumulation of parent drug and its metabolite(s).**
- **The accumulation of metabolites and toxic end-products of intermediary metabolism seen in CKD, may affect the disposition of other drugs.**

Pharmacokinetic Changes In CKD

- **Some metabolites may have pharmacologic activity similar to that of the parent drug:**

a. **Oxypurinol is an active metabolite of allopurinol**

b. **Morphine is metabolized to the active metabolites morphine-3- glucuronide and morphine-6-glucuronide which readily cross the blood-brain barrier and bind to opiate receptors, exerting strong analgesic effects.**

Pharmacokinetic Changes In CKD

- **The metabolite may have dissimilar pharmacologic action (norpethidine has CNS stimulatory activity that produces seizures, whereas pethidine has CNS depressant actions).**

Pharmacodynamic Changes In CKD

- **In CKD, the response to a given drug many change beyond that predicted by pharmacokinetic changes alone.**
- **For example, uremic toxins' accumulation may cause complex disturbances of the coagulation system leading to increased bleeding.**
- **Therefore, enoxaparin dosage adjustment based on creatinine clearance may NOT lead to optimal anticoagulation.**

Estimation of Kidney Function for Drug Dosage Regimen Individualization

- **Accurate assessment of kidney function is needed for appropriate drug dosing regimens.**

Methods:

1. **Accurate measurement of GFR (creatinine clearance) as you see in the clinical setting.**
2. **Use of equations derived by epidemiological studies. Many of these are available for different populations of patients.**

Estimation of Kidney Function for Drug Dosage Regimen Individualization

- You should be aware that these equations are only approximations, and other patient factors should be considered.
- Then, the maintenance dose (MD) can be calculated according to renal clearance taking into consideration the presence of non-renal clearance of the drug.

$$MD = Cl_T \times \text{Desired } C_{ss}$$

Relationship Between CL_{cr} and CL of Select Drugs

Drug	Total Body Clearance
Amikacin	CL = 0.6 (CLcr) + 9.6
Gentamicin	CL = 0.983 (CLcr)
Ciprofloxacin	CL = 2.83 (CLcr) + 363
Digoxin	CL = 0.88 (CLcr) + 23
Imipenem	CL = 1.42 (CLcr) + 54
Lithium	CL = 0.20 (CLcr)
Piperacillin	CL = 1.36 (CLcr) + 1.50
Vancomycin	CL = 0.69 (CLcr) + 3.7

References for Drug Dosing in CKD

1. Aronoff's Drug Prescribing in Renal Failure.
2. The Renal Drug Handbook.
3. Lexicomp.
4. Micromedex.
5. American Hospital Formulary Service.

Dosing Adjustments

Methods for maintenance dosing adjustments:

- **Dose reduction, lengthening the dosing interval, or both.**

1. **Dose reduction involves reducing each dose while maintaining the normal dosing interval.**

- **This approach maintains more constant drug concentrations, but is associated with a higher risk of toxicities if the dosing interval is inadequate to allow for drug elimination.**

Dosing Adjustments

2. **Normal doses are maintained, but the dosing interval is prolonged to allow time for drug elimination before re-dosing.**

- **Prolongation of the dosing interval is associated with a lower risk of toxicities but a higher risk of subtherapeutic drug concentrations, especially toward the end of the dosing interval.**

Dosing Adjustments

1. **Diuretics:**

- **Thiazide diuretics are considered first-line treatment for patients with uncomplicated hypertension and CKD (only if Scr < 2.5 mg/dL or CrCl > 30 mL/min).**
- **Loop diuretics are also commonly used to treat uncomplicated hypertension in CKD patients.**
- **Potassium-sparing diuretics should be avoided because potassium is dangerous to these patients.**

Dosing Adjustments

2. **Antihypertensives:**

- **Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers are first-line antihypertensives used in patients with type 1 or 2 diabetes and early CKD.**
- **Hydrophilic β-blockers (atenolol, bisoprolol, and nadolol) require dosing adjustments in CKD patients.**

Dosing Adjustments

3. **Antihyperglycemic Agents:**

- **A renally-excreted agent like metformin is not recommended if Scr is >1.5 mg/dL in men or >1.4 mg/dL in women.**
- **It is important to monitor CKD patients on metformin closely for lactic acidosis development.**
- **Sulfonylureas (chlorpropamide and glyburide) should be avoided in patients with stage 3 - 5 CKD, as their use increases hypoglycemia risk.**

Dosing Adjustments

4. **Analgesics:**

- **Metabolites of morphine, tramadol, and codeine can accumulate in CKD patients, leading to respiratory depression.**
- **Dosage reduction is recommended for morphine and codeine in patients with CrCl < 50 mL/min.**
- **Metabolite accumulation can lead to supra-therapeutic concentrations and cause toxicity.**
- **Dosing intervals for opioids may need to be modified in CKD patients.**

Dosing Adjustments

5. **Statins:**

- **Statin therapy for dyslipidemia is commonly used in CKD patients.**

a. **Atorvastatin has NO dose adjustment recommendation.**

b. **Rosuvastatin, simvastatin, and lovastatin need dose adjustment**

c. **Fluvastatin should be used with caution in CKD patients.**

Dosing Adjustments

- **The following slides might be used as resource information for dose adjustment in CKD.**

Dosing Requirements of Select Drugs in Patients with Chronic Kidney Disease

Drug	Usual Dose	Percent of usual dose	
		GFR 10-50	GFR < 10
ACE-inhibitors			
Enalapril	5-10 mg q12 hours	50-100%	50%
Lisinopril	5-10 mg daily	50-75%	25-50%
β-Blockers			
Atenolol	50-100 mg daily	50%	25%
Bisoprolol	10 mg daily	75%	50%
Diuretics			
Amiloride	5 mg daily	50%	Avoid
Spironolactone	50-100 mg daily	10 mg daily max (watch for hyperkalemia)	Avoid
Furosemide & bumetanide		No adjustment needed	
Thiazide	25-50 mg daily	100%	Avoid
Triamterene	50-100 mg twice daily	100% (watch for hyperkalemia)	Avoid

Antidiabetic drugs			
Glipizide	5 mg daily	No dose adjustment needed	
Glyburide	2.5-5 mg daily	Avoid	Avoid
Metformin		Monitor for lactic acidosis) Avoid if Cr_{sr} > 1.5 mg/dl in males or > 1.4 mg/dl in females, patients older than 80 years with chronic heart failure. It should be temporarily discontinued for 24-48 hours before use of iodinated contrast media, and restarted for 48 hours afterward. May be started only when renal function has normalized.	

Antifungals			
Fluconazole	200-400 mg daily	50%	50%
Itraconazole	100-200 mg q 12 hours	100%	50% (IV form contraindicated)
Miconazole		No adjustment needed	

Antibiotics			
Imipenem	0.25-1 g q 6 hours	50%	25%
Meropenem	1-2 g q 8 hours	50% q 12 hours	50% q 24 hours
Cefazolin	0.25-2 g q 6 hours	0.25-2 g q 12 hours	50% q 24-48 hours
Cefepime	0.25-2 g q 8-12 hours	50-100% q 24 hours	25-50% q 24 hours
Cefixime	200 mg q 12 hours	75%	50%
Cefotaxime	1-2 g q 6-12 hours	q 6-12	50%
Cefotetan	1-2 g q 12 hours	q 24 hours	q 48 hours
Ceftazidime	1-2 g q 8 hours	q 12-24 hours	q 24-48 hours
Ceftriaxone	No adjustment needed		
Cefuroxime	0.75-1.5 g q 8 hours	q 8-12 hours	q 12 hours
Cephalexin	250-500 mg q 6-8 hours	q 8-12 hours	Q 12-24 hours
Clarithromycin	250-500 mg q 12 hours	50-100%	50%
Penicillin G	0.5-4 million U q 4-6 hours	75%	50%

Piperacillin/tazobactam	3.375-4.5 g q 6-8 hours	2.25-g q 6-8 hours	2.25 g q 8 hours
Ticarcillin/clavulanate	3.1g q 4 hours	q 8-12 hours	2 g q 12 hours
Ciprofloxacin	400 mg IV q 12 hours	50-75%	50%
	500-750 mg orally q 12 hours	50-75%	50%
Gemifloxacin	320 mg q 24 hours	50-100%	50%
Levofloxacin	250-750 mg Q24 hours	500-750 mg initial dose, then 250-750 mg Q 24-48 hours	500 mg initial dose, then 250-500 mg Q 48 hours
Moxifloxacin		No dose adjustment needed	
Sulfamethoxazole	1 g q 8-12 hours	q 18 hours	q 24 hours
Trimethoprim	100 mg q 12 hours	q 12-18 hours	q 24 hours
Doxycycline		No dose adjustment needed	
Clindamycin		No dose adjustment needed	
Nitrofurantoin	500-1000 mg q 6 hours	Avoid	Avoid

Statins			
Atorvastatin	10 mg daily	No dose adjustment needed	
Lovastatin	20-40 mg daily	Use with caution when GFR <30 ml/min	
Rosuvastatin	5-40 mg daily	5 mg daily in patients with GFR <30 ml/min, no to exceed 10 mg	
Simvastatin	10-20 mg daily	5 mg daily in patients with GFR <10 ml/min.	
Other drugs			
Allopurinol	300 mg daily	50%	25%
Famotidine	20-40 mg at bedtime	25%	10%
Gabapentin	300-600 mg q 8 hours	400-1400 mg twice daily, when GFR > 30-59 ml/min. 200-700 mg daily when GFR > 15-29 ml/min.	100-300 mg daily
Metoclopramide	10-15 mg 3 times daily	75%	50%

Drug Use in Hepatic Disease

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Considerations in Hepatic Disease

- **The impact on drug metabolism in liver diseases is greater for phase I (oxidation) than phase II reactions (conjugation).**
- **Some CYP enzymes are more affected than others.**
- **Glucuronidation in liver disease is relatively spared, but NOT for all drugs.**

Considerations in Hepatic Disease

- **Cholestasis is associated with reduction of CYP enzymes.**
- **Hepatic disease can alter the pharmacokinetics of drugs including absorption and disposition; and pharmacodynamics including efficacy and safety.**
- **Drugs are often metabolized by one or more enzymes in the liver.**
- **Drugs and metabolites may also be excreted in bile.**

Considerations in Hepatic Disease

- **Drugs with flow-dependent clearance should be avoided if possible in patients with liver failure.**
- **Doses of such drugs may need to be reduced to as low as one-tenth of the conventional dose, for an orally administered agent.**
- **Starting therapy with low doses and monitoring response or plasma levels provides the best opportunity for safe, effective treatment.**

Considerations in Hepatic Disease

Hepatic disease may lead to:

a. **drug accumulation**
b. **failure to form an active or inactive metabolite**
c. **increased bioavailability after oral administration**
d. **reductions in drug–protein binding.**

- **Liver disease may affect kidney function, which can lead to accumulation of a drug and/or its metabolites even when the liver is NOT primarily responsible for elimination.**

Considerations in Hepatic Disease

- **In contrast to creatinine clearance which has been used successfully to measure kidney function and renal clearance of drugs, there is NO such test to estimate hepatic drug clearance in patients with hepatic disease.**
- **Liver disease affects the quantitative and qualitative synthesis of albumin, globulins, and other circulating plasma proteins that might affect plasma drug protein binding and distribution.**

Considerations in Hepatic Disease

Plasma Protein Binding:

- **Adjustment of phenytoin concentration in hypoalbuminemia:**
- $C_{normal} = C_{observed} / [0.2 (albumin) + 0.1]$

Active Drug and Its Active Metabolite

1. **When the drug is more potent than the metabolite, the overall pharmacologic activity will increase in the hepatic-impaired patient because the parent drug concentration will be higher.**
2. **When the drug is less potent than the metabolite, the overall pharmacologic activity in the hepatic patient will decrease because less of the active metabolite is formed.**

Considerations in Hepatic Disease

- Patients with hepatic cirrhosis are ~ 2-5 times more prone to adverse drug reactions than patients without hepatic dysfunction.
- This might be due to pharmacodynamic and pharmacokinetic changes.
- Little information is available on pharmacodynamic changes.
- Central nervous system sensitivity is increased for morphine, chlorpromazine, and diazepam.

Considerations in Hepatic Disease

- **Hepatic encephalopathy can be precipitated by sedatives, analgesics and tranquilizers; and much more so by diuretics.**
- **Changes in pharmacologic activity due to hepatic disease may be much more complex when both the pharmacokinetic parameters and the pharmacodynamics of the drug change as a result of the disease process.**

Recommendations for select drug dosage change in patients with chronic liver disease.

Drug	Metabolism	Recommendation
Acetaminophen (Paracetamol)	Conjugation	Do NOT Exceed 2g/day
Allopurinol	Oxidation (active metabolite	Reduce dose 50%
Amitriptyline	Oxidation, conjugation	Start at 50% of normal dose, then adjust and monitor for clinical & adverse effect
Amlodipine	Extensive oxidation	Precaution
Azathioprine	Oxidation	Precaution

Carbamazepine	Oxidation, active metabolite, glucuronidation	Avoid, it worsen liver disease
Clindamycin	Extensive oxidation, active metabolite	Prolong dosing interval, monitor hepatic function
Clomipramine	Oxidation, glucuronidation	Avoid
Codeine	Extensive oxidation, active metabolite (morphine)	Avoid
Cyclophosphamide	Hydroxylation	Reduce dose 25%, monitor hepatic function

Cyclosporine	Oxidation to several metabolites	Precaution, measure drug level in whole blood
Dacarbazine	Extensive oxidation, toxic metabolites	Reduce dose 25-50%, monitor serum level
Daunorubicin	Cytotoxic metabolites, conjugation	Reduce dose 25-50%
Diazepam	Extensive oxidation, active metabolites	Reduce dose 50%, or use lorazepam
Doxycycline	Metabolized	Precaution, use other antibiotics
Enalpril	Active metabolites	Precaution

Erythromycin	Extensive oxidation	Reduce dose 30-50 %, Prolong interval to 8 hours
Fluoxetine	Oxidation, active metabolites	Reduce dose 50%
Fluphenazine	Oxidation, conjugation	Avoid
Glibenclamide	Extensive metabolism	Start with 1.25 mg and monitor effect
Ibuprofen	Extensive metabolism	Precaution
Isoniazid	Extensive metabolism	Contraindicated
Itraconazole	Extensive metabolism	Precaution
Lidocaine	Extensive metabolism	Avoid
Mefloquine	Extensive metabolism	Avoid

Metformin	No metabolism	Avoid
Methotrexate	Little metabolism	Avoid, contraindicated
Methyldopa	Metabolized 50%	Precaution
Metronidazole	Metabolized 50%, oxidation	250 mg/8hours
Morphine	Glucuronidation	Avoid
Phenytoin	Oxidation, glucuronidation	Increases liver toxicity, monitor, avoid
Phenobarbital	Oxidation, glucuronidation	Avoid
Pyrazinamide	Metabolized 95%	Precaution, monitor liver function, avoid

Rifampin	Liver metabolism, active metabolites	Max. dose 6-8mg/kg twice a week
Simvastatin	Extensive oxidation	Precaution
Trimethoprim/ sulfametoxazole	Oxidation, acetylation	Precaution
Valproic acid	Extensive oxidation, glucuronidation	Reduce dose 50%, monitor serum level
Verapamil	Extensive oxidation	Reduce 50% IV dose, and 20% oral dose
Vinblastine, vincristine	Extensive oxidation, biliary excretion	Reduce dose 50%
Voriconazole	Extensive oxidation	Reduce dose, prolong interval, or avoid
Warfarin	Extensive oxidation	Monitor INR

Therapy of Epilepsy

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Therapy of Epilepsy

- There are many types of epilepsies characterized by different seizure types, with differences in severity and etiologies.
- In all epilepsies, there is disrupted regulation of electrical activity in the brain resulting in synchronized and excessive neuronal discharge.
- Accurate classification and diagnosis of seizure type, including mode of seizure onset, is critical to selection of appropriate pharmacotherapy.

Therapy of Epilepsy

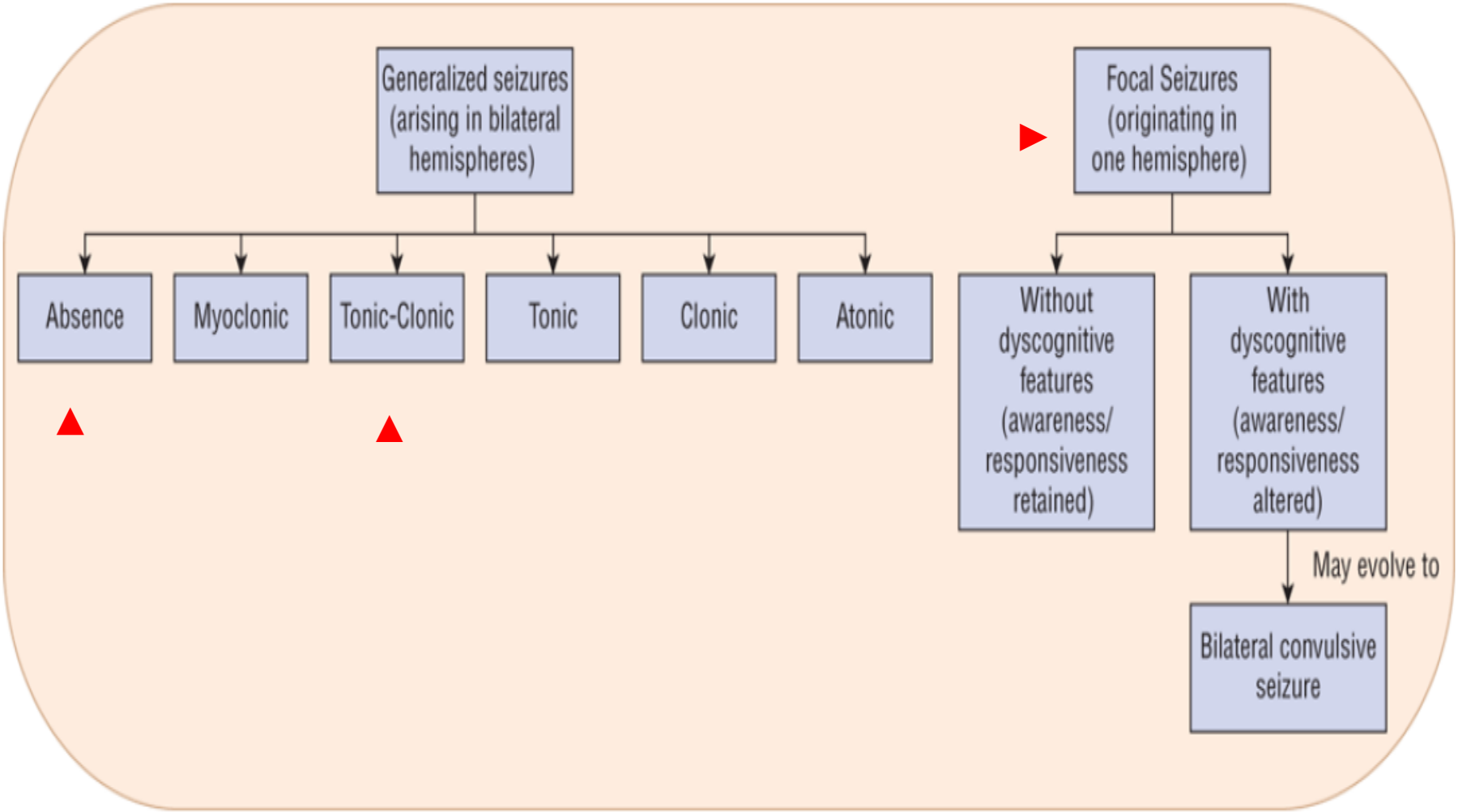
Aims of Drug therapy:

a) **Reducing the frequency of seizures as much as possible.**
b) **Minimizing adverse effects of antiseizure drugs.**
c) **Addressing coexisting health and social conditions.**
d) **Enhancing quality of life (QOL).**

Therapy of Epilepsy

- **Some seizures are provoked by infections, fever (febrile seizures), drug overdose, alcohol, barbiturate or benzodiazepine withdrawal, brain hemorrhage, hypocalcemia, hypoglycemia, uremia, and eclampsia.**
- **These seizures do NOT constitute epilepsy, they disappear once the provoking insult is removed or treated.**

2010 ILAE Revised Terminology for Classification of Seizures.



Source: J.T. DiPiro, R.L. Talbert, G.C. Yee, G.R. Matzke, B.G. Wells, L.M. Posey: Pharmacotherapy: A Pathophysiologic Approach, 10th Edition, www.accesspharmacy.com

Therapy of Epilepsy

Treatment:

- **Anti-seizure drug (ASD) therapy is the mainstay of epilepsy treatment.**
- **ASDs provide symptomatic treatment only.**
- **They have NO disease modifying properties, and are NOT curative.**
- **Drugs act to prevent seizures mainly.**
- **Therapy is usually life-long.**

Therapy of Epilepsy

- **Remember that the goal of ASD therapy is to eliminate seizures with minimal adverse effects.**
- **In 20% to 35% of patients this may NOT be possible, and seizure control must be balanced with QOL goals.**
- **For those who can NOT obtain seizure freedom despite these therapies, a decrease in the number of seizures with minimized drug adverse effects will be a reasonable goal.**

Therapy of Epilepsy

If the therapeutic goal is NOT achieved with monotherapy:

1. **Add a second antiseizure drug (ASD), preferably with a different mechanism of action.**
2. **Or switch to an alternative single ASD.**

- **Emphasize treatment with a single drug.**

Therapy of Epilepsy

- **The drug treatment of first-choice depends on the type of epilepsy; and patient characteristics such as age, gender, co-morbid medical conditions, susceptibility to adverse effects, ability to comply with a prescribed regimen.**
- **Once the proper ASD is selected, patient education and understanding of the treatment plan is essential.**

Therapy of Epilepsy

- **The single most common reason for treatment failure is medication non-adherence.**
- **Up to 60% of patients with epilepsy are non-adherent to therapy.**

Reasons for non-adherence:

1) **Financial constraints.**
2) **Complexity of the drug regimen.**
3) **Frequent uncontrolled seizures.**

Therapy of Epilepsy

- **Anti-seizure drug withdrawal should be gradual, to avoid recurrence of seizures. Sudden withdrawal can be associated with "Status Epilepticus".**
- **Withdrawal seizures are more common with benzodiazepines and barbiturates, which should be withdrawn more slowly over a period of many months.**

Therapy of Epilepsy

Pharmacologic Therapy:

- **An ASD must be effective for the specific seizure type.**
- **Individualization of therapy is important.**
- **A patient may be better suited to receive one drug over the other, because of susceptibility for certain adverse effects or the presence of co-morbid conditions.**

Therapy of Epilepsy

- **Patient characteristics such as age, gender, and medical conditions must be considered:**

1. **Children may be more susceptible to neuropsychiatric adverse effects.**
2. **Women of child-bearing potential should not receive teratogenic drugs.**
3. **The elderly may be more susceptible to adverse effects on cognition, therefore, avoid drugs that affect cognition.**

Therapy of Epilepsy

4. **Patients with co-morbid conditions (migraine headache, tremor, or neuropathy) may benefit from the use of a drug that can also treat the other condition.**

- ** **Extreme attention should be paid to drug-drug interactions with other drugs, and among ASDs themselves.**

Therapy of Epilepsy

1. **Select one ASD, start with a low dose, and gradually titrate to a moderate dose goal, taking into account the patient's response to treatment.**
- **If the patient is seizure free with NO adverse effects at a moderate therapeutic dose, then NO further increase in dose is necessary.**
2. **If there is NO adequate response at that dose, attempt increasing the dose.**

Therapy of Epilepsy

3. **If the first ASD monotherapy is still ineffective, or if the patient experiences intolerable adverse effects, adding a second ASD with a different mechanism of action and then tapering and discontinuing the first ASD is appropriate.**
4. **If the second ASD is ineffective, combination therapy may be indicated (although NOT desirable).**

Therapy of Epilepsy

5. In elderly patients who are sensitive to falls, sedation, and neuro-cognitive adverse effects, start at much lower initial dose and then titrate slowly (weeks – months), with a lower maximum dose goal.
6. In patients with multiple recent seizures, a therapeutic dose needs to be reached much more quickly, and a more rapid titration over days instead of weeks is appropriate.

Therapy of Epilepsy

Effectiveness of ASDs:

- **Some ASDs including carbamazepine, ethosuximide, gabapentin, levetiracetam, oxcarbazepine, phenytoin, valproic acid, and zonisamide, have strong-enough evidence to be labeled as effective, or as probably effective as initial monotherapy in certain seizure types.**
- **Others have weaker evidence and can only be labeled as possibly or potentially effective.**

Therapy of Epilepsy

Drug Resistance:

- **Drug resistance is defined as "failure of two tolerated and appropriately chosen ASD (as monotherapy or in combination) to achieve sustained seizure freedom."**
- **Approximately 65% of patients can be maintained on one ASD and considered well controlled, although NOT necessarily seizure free.**

Therapy of Epilepsy

- **The percentage of patients who are seizure-free on one drug after 12 months of treatment varies:**

a) **For only generalized tonic-clonic seizures (~ 50 %).**

b) **For only focal seizures (~ 25%).**

c) **For those with mixed seizure types (~ 25%).**

Therapy of Epilepsy

- **Of the 35% of patients with unsatisfactory control on monotherapy, 10% will be well controlled with a two-drug combination.**
- **Of the remaining 25%, 20% will continue to have unsatisfactory control despite greater than two drug treatment and are considered drug-resistant.**

Pharmacokinetics and Drug-Drug Interactions

- Knowledge of ASD inducer or inhibitory effects on drug metabolizing enzymes is needed for the optimization of ASD therapy.
- Pharmacokinetic interactions are a common and serious complicating factor in ASD selection.
- Inducers include: carbamazepine, lamotrigine, phenytoin, phenobarbital, vigabatrin.
- Inhibitors include: valproic acid, topiramate.

Pharmacokinetics and Drug-Drug Interactions

- **Caution should be experienced when any ASD is added to or withdrawn from a drug regimen.**
- **Knowledge of the presence of active metabolites of ASDs is important as they affect duration of action of the drug: carbamazepine, primidone.**
- **Drugs with toxic metabolites include valproic acid.**

Adverse Effects

Some common adverse effects shared by ASDs:

1. **CNS adverse effects are among the most common effects of ASDs and include sedation, dizziness, blurred or double vision, difficulty in concentration, and ataxia.**
2. **Impairment of cognition: barbiturates cause more cognitive impairment than any other ASDs.**

- **(in children barbiturates paradoxically cause hyperactivity).**

Adverse Effects

- **In general, newer agents have less effects on cognition. (except topiramate which causes substantial cognitive impairment).**
- **These effects can be avoided by titrating the dose upward very slowly, or can be improved by decreasing the dose.**
- **Patients switched from polytherapy to monotherapy may also demonstrate improvement in cognition.**

Adverse Effects

3. **Osteomalacia and osteoporosis:**

- **Phenytoin, phenobarbital, carbamazepine, oxcarbazepine, ~~felbamate~~, and valproic acid, may interfere with vitamin D metabolism.**
- **Patients receiving these drugs should have:**

a. **Supplemental vitamin D and calcium.**

b. **Bone mineral density testing if other risk factors for osteoporosis are present.**

Role of Serum Concentration Monitoring

- **Monitoring of the older ASDs is used to optimize therapy for an individual patient, but NOT as a therapeutic end point in itself.**
- **The serum concentration result should be interpreted in association with clinical response.**
- **Seizure control can occur before the "minimum" of the therapeutic range is achieved, and adverse effects can appear before the "maximum" of the range is achieved.**

Role of Serum Concentration Monitoring

- **Higher concentrations are needed to control focal dyscognitive seizures than to control tonic–clonic seizures.**

Serum levels can also be useful:

a. **To document lack or loss of efficacy.**
b. **To document non-adherance.**
c. **To determine how much room there is to increase a dose based on expected toxicity.**

Role of Serum Concentration Monitoring

d. In patients with significant renal or hepatic dysfunction.
e. In those taking multiple drugs.
f. In women who are pregnant or taking oral contraceptives.

- Monitoring should be performed only at steady-state.
- Therapeutic concentration ranges have NOT been clearly defined for some of the second-generation ASDs.

Antiseizure Drug Pharmacokinetic Data

ASD	Time to Steady-State (Days)	Active Metabolite	Protein binding (%)
Carbamazepine	21-28, for completion of autoinduction	10,11-epoxide	40-90
Clobazam	7-14	N-desmethylclobazam	80-90
Eslicarbazepine	4-5	Oxcarbazepine	
Ethosuximide	6-12	--	
Ezogabine	3-4	N-acetyl metabolite	80
Felbamate	5-7	--	
Gabapentin	1-2	--	
Lacosamide	3	--	
Lamotrigine	3-15	--	
Levetiracetam	2	--	
Oxcarbazepine	2	10-hydroxycarbazepine	
Perampanel	14-21	--	95
Phenobarbital	14-21	--	
Phenytoin	7-28	--	90
Pregabalin	1-2	--	
Primidone	1-4	Phenobarbital	
Rufinamide	2	--	
Tiagabine		--	95
Topiramate	4-5	--	
Valproic acid	1-3	toxic	90-95, Saturable
Vigabatrin		--	
Zonisamide	5-15	--	

Antiseizyure Drugs Target Serum Concentration Ranges

Drug	Target Concentration Range
Phenobarbital	10 - 40 µg/mL
Clobazam	0.03 - 0.3 ng/mL
Clonazepam	20 - 70 ng/mL
Phenytoin	10 - 20 µg/mL
Ethosuximide	40 - 100 µg/mL
Carbamazepine	4 - 12 µg/mL
Gabapentin	2 - 20 µg/mL
Lamotrigine	4 - 20 µg/mL
Levetiracetam	12- 46 µg/mL
Tiagabine	0.02 - 0.2 µg/mL
Topimarate	5 - 20 µg/mL
Valproic acid	50 - 100 µg/mL
Vigabatrin	0.8 - 36 µg/mL
Zonisamide	10 - 40 µg/mL

Evaluation of Therapeutic Outcomes

1. **Clinical response is more important than the serum drug concentrations and involves:**

a. **Identifying the type and number of seizures.**

b. **Identifying drug adverse effects.**

2. **Patients should record the severity and the frequency of seizures.**

3. **Ascertain if the patient is truly seizure free.**

Evaluation of Therapeutic Outcomes

4. **Monitor patient long-term for co-morbid conditions, social adjustment (including Quality-Of-Life assessments), drug interactions, and adherence.**
5. **Screen periodically for co-morbid neuropsychiatric disorders (depression and anxiety).**

Personalized Pharmacotherapy

- **The most important aspect of ASD use is individualization of therapy.**
- **The following should be considered together:**

1. **Seizure type.**
2. **Concomitant medical problems (hepatic function, renal function, psychiatric diseases, other neurologic problems, …).**
3. **Concurrent medications.**
4. **Patient specific characteristics (age, gender, child-bearing ability, and ethnicity).**

Therapeutic Considerations in the Elderly

1. **The elderly are often on polytherapy which may contribute to:**

a. **Increased sensitivity to neuro-cognitive effects.**

b. **Increased possibility of drug-drug interactions with ASDs that affect the cytochrome P450 (CYP450) system (carbamazepine, phenytoin, and valproic acid, …).**

Therapeutic Considerations in the Elderly

2. Hypoalbuminemia is common in the elderly which may cause problems with highly bound ASD (phenytoin, valproic acid, …).
3. The elderly experience body mass changes, such as an increase in fat to lean body mass or decrease in body water, which can affect the drug volume of distribution and elimination half-life.

Therapeutic Considerations in the Elderly

4. **The elderly may have compromised renal or hepatic function that require ASD dosage adjustment.**

- **Lamotrigine is considered the medication of choice in elderly, because it has equal efficacy to carbamazepine and gabapentin, and is better tolerated than carbamazepine.**

Therapeutic Considerations in the Young

- **For neonates and infants, an increase in the total body water to fat ratio and a decrease in serum albumin and α-acid glycoprotein can result in volume of distribution changes that affect ASD elimination half-life.**
- **Children up to the age of 3 years have decreased renal elimination of ASDs, especially in neonates.**

Therapeutic Considerations in the Young

- **Hepatic activity is reduced in neonates and infants, but by age 2 to 3 years it becomes more than that of adults.**
- **Therefore, neonates and infants require lower doses of ASDs, while children require higher doses than adults (based on body weight).**
- **Therapeutic drug monitoring is especially important in the young (but the therapeutic blood levels range is NOT well-defined as in adults).**

Therapeutic Considerations in Women

- Some women develop "catamenial seizures" (just before and during the menstrual flow and at the time of ovulation), which may be due to a slight increase of estrogen relative to progesterone, or due to progesterone withdrawal.
- The risk is ~ 10% - 70% in women with epilepsy.
- Treatment: conventional ASDs are the primary agents.

Therapeutic Considerations in Women

- At menopause, seizures improve in frequency, particularly the catamenial seizures.
- Enzyme-inducing ASDs increase the metabolism of estrogen, progesterone, and testosterone.
- They also increase production of sex hormone-binding globulin, leading to decreases in the free fraction of these hormones.
- All of this may lead to menstrual irregularity, infertility, sexual dysfunction, and polycystic ovary syndrome (PCOS).

Therapeutic Considerations in Women

- **Enzyme-inducing ASDs can cause treatment failures in women taking oral contraceptives due to increased metabolism of ethinyl estradiol and progestin.**
- **Valproic acid may affect sex hormone concentrations causing hyper-androgenism and polycystic changes.**

Therapeutic Considerations in Men

- Men with epilepsy have reduced fertility.
- Carbamazepine, oxcarbazepine, and valproic acid are associated with sperm abnormalities in men.
- Valproic acid may cause testicular atrophy resulting in reduced testosterone levels.
- Various ASDs may affect libido and sexual function in both men and women.

Clinical Considerations with Specific Drugs

Carbamazepine:

Mechanism of Action :

- **It enhances fast inactivation of voltage-gated Na^+ channels.**

Place in Therapy:

- **It is considered first-line in many seizure types: focal onset seizures, generalized tonic-clonic seizures, and mixed seizure types.**

Clinical Considerations with Specific Drugs

- It may worsen absence seizures, and precipitate tonic-clonic seizures in patients with other generalized seizure types.

Drug Interactions:

1. Carbamazepine induces the metabolism of primidone, phenytoin, ethosuximide, valproic acid, and clonazepam.
2. Phenytoin and phenobarbital decrease steady-state concentration of carbamazepine by enzyme induction.

Clinical Considerations with Specific Drugs

3. **Propoxyphene, troleandomycin, and valproic acid may inhibit carbamazepine clearance and increase its steady-state levels.**
4. **CYP3A4 inhibitors may potentially increase carbamazepine serum concentrations.**

Important Adverse Reactions:

A. Concentration-dependent:

- **Diplopia, dizziness, unsteadiness, drowsiness, nausea.**

Clinical Considerations with Specific Drugs

B. Idiosyncratic:

- **Blood dyscrasias, Steven-Johnson syndrome or epidermal necrolysis.**

C. Chronic:

- **Hyponatremia, metabolic bone disease (monitor serum calcium and vitamin D).**

Clinical Considerations with Specific Drugs

Phenytoin:

Mechanism of Action:

- It inhibits voltage-gated Na^+ channels.

Place in Therapy:

- Phenytoin is used for focal onset seizures and generalized tonic-clonic seizures.
- At very high concentrations of greater than 50 µg/mL, it can exacerbate seizures.

Clinical Considerations with Specific Drugs

Pharmacokinetics:

- **The oral absorption of phenytoin may be saturable at doses above 400 mg/day.**
- **Phenytoin is highly protein bound, and it is essential to know the patient's serum albumin level when interpreting serum phenytoin concentrations.**
- **Significant renal dysfunction will also alter phenytoin protein binding.**
- **It distributes to breast milk and it crosses the placenta.**

Clinical Considerations with Specific Drugs

- **Phenytoin displays Michaelis–Menten pharmacokinetics, (or zero-order kinetics).**

  The metabolism of phenytoin saturates at doses used clinically, so that a small change in dose can result in a disproportionally large increase in serum concentrations, potentially leading to toxicity.

Clinical Considerations with Specific Drugs

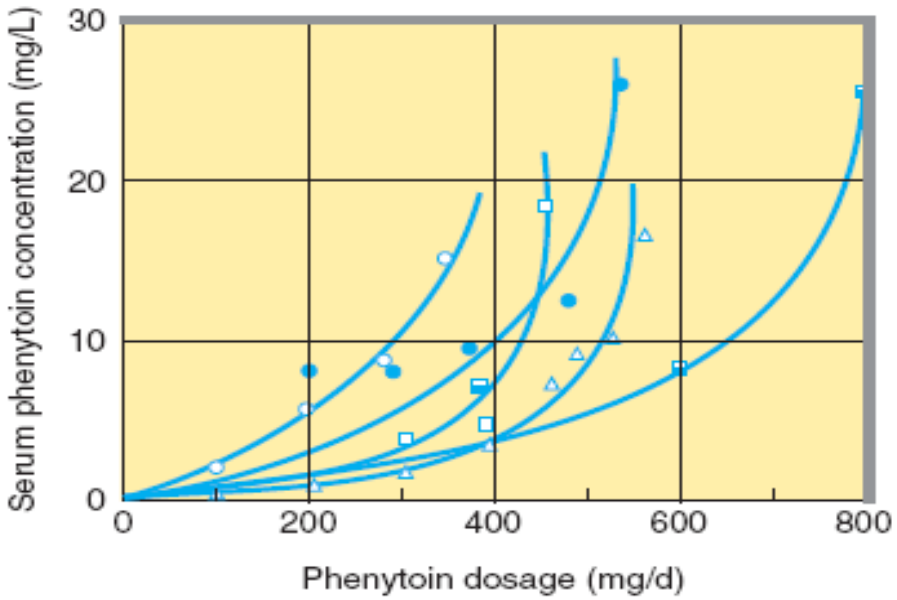


FIGURE 24–5 Nonlinear relationship of phenytoin dosage and plasma concentrations. Five patients (identified by different symbols) received increasing dosages of phenytoin by mouth, and the steady-state serum concentration was measured at each dosage. The curves are not linear, since, as the dosage increases, the metabolism is saturable. Note also the marked variation among patients in the serum levels achieved at any dosage. (Modified, with permission, from Jusko WJ: Bioavailability and disposition kinetics of phenytoin in man. In: Kellaway P, Peterson I [editors]: *Quantitative Analytic Studies in Epilepsy.* Raven Press, 1977.)

Clinical Considerations with Specific Drugs

Drug Interactions:

1. **Phenytoin is an inducer of both CYP450 and UGT isozymes (which conjugate drugs with glucuronic acid).**
2. **It decreases folic acid absorption.**

- **Folic acid replacement can reduce phenytoin concentration and result in loss of efficacy.**

3. **Phenylbutazone and sulfonamides can displace phenytoin from binding sites to plasma proteins.**

Clinical Considerations with Specific Drugs

- **Hypoalbuminemia results in decreased total plasma drug concentration but NOT necesserily the free concentration.**
- **In these 2 cases intoxication may occur if total drug levels are increased by increasing the dose.**

4. **Phenobarbital and carbamazepine induce the metabolism of phenytoin.**
5. **Isoniazid inhibits the metabolism of phenytoin.**

Clinical Considerations with Specific Drugs

Important Adverse Reactions:

A. Concentration-dependent:

- **Diplopia, blurring of vision, nystagmus, ataxia, dizziness, somnolence, incoordination, sedation, behavioral changes, cognitive impairment, fatigue.**

B. Idiosyncratic:

- **Blood dyscrasias, Steven-Johnson syndrome or epidermal necrolysis, pseudolymphoma.**

C. Chronic:

- **Cerebellar syndrome, connective tissue changes, skin thickening, folate deficiency, gingival hyperplasia, hirsuitism, coarsening of facial features, acne, metabolic bone disease (monitor serum calcium and vitamin D).**

Clinical Considerations with Specific Drugs

Valproic Acid:

Mechanism of Action:

- **It may potentiate postsynaptic GABA responses.**

Place in Therapy:

- **Valproic acid is first-line therapy for generalized seizures, including myoclonic, atonic, and absence seizures.**
- **It is also used in migraine headache and bipolar disorders.**

Clinical Considerations with Specific Drugs

Pharmacokinetics:

- **Valproic acid is extensively bound to albumin, and binding is saturable at high concentrations, or in patients with hypoalbuminemia.**
- **The primary pathway of valproic acid metabolism is β-oxidation, then glucuronidation.**
- **One of its metabolites (4-ene-VPA) may be increased with enzyme-inducing drugs, and may cause hepatotoxicity.**
- **It crosses into the placenta and attains high concentrations in fetal circulation (Teratogenic).**

Clinical Considerations with Specific Drugs

Drug Interactions:

1. **Highly protein-bound drugs (free fatty acids, phenytoin, aspirin) can displace valproic acid.**
2. **It displaces phenytoin from plasma proteins.**
3. **It can inhibit specific CYP450 isozymes, epoxide hydrolase, and UGT isozymes.**
4. **It inhibits the metabolism of phenobarbital, phenytoin, carbamazepine, lamotrigine and other drugs.**

Clinical Considerations with Specific Drugs

5. **Oral contraceptives may increase the clearance of valproic acid and lower serum levels by 20%.**
6. **Meropenem can lower valproic acid levels.**

Clinical Considerations with Specific Drugs

Important Adverse Reactions:

A. Concentration-dependent:

- **GI upset, sedation, unsteadiness, tremor, thrombocytopenia.**

B. Idiosyncratic:

- **Acute hepatic failure, acute pancreatitis, alopecia.**

C. Chronic:

- **Polycystic ovary syndrome, weight gain, menstrual cycle irregularities, hyperammonemia.**

Clinical Considerations with Specific Drugs

Ethosuximide:

Mechanism of Action:

- **Inhibition of T-type Ca^{2+} channels.**

Place in Therapy:

- **It is a first-line treatment for absence seizures. It has a very narrow spectrum of activity.**

Drug Interactions:

- **Valproic acid may inhibit ethosuximide's metabolism, when the metabolism of ethosuximide is near saturation.**

Clinical Considerations with Specific Drugs

Important Adverse Reactions:

A. Concentration-dependent:

- **Ataxia, drowsiness, GI upset, unsteadiness, hiccoughs.**

B. Idiosyncratic:

- **Blood dyscrasia, rash.**

C. Chronic:

- **Behavioral changes, headache.**

Clinical Considerations with Specific Drugs

Lamotrigine:

Mechanism of Action:

- **Lamotrigine inhibits voltage-gated Na^+ channels.**
- **It modulates high voltage-gated Ca^{2+} channels.**
- **It modulates hyperpolarization-activated cation channels.**
- **It attenuates release of glutamate and to a lesser extent, GABA and dopamine.**

Clinical Considerations with Specific Drugs

Place in Therapy:

1. **Monotherapy and adjunctive treatment in patients with focal onset seizures, as a first- or second-line therapy.**
2. **It is used in primary generalized tonic-clonic seizures and for primary generalized seizures of Lennox-Gastaut Syndrome (LGS).**

- **Its half-life is prolonged in renal failure, and is dialyzable.**

Clinical Considerations with Specific Drugs

Drug Interactions:

- **Valproic acid inhibits Its metabolism.**
- **Carbamazepine increased its CNS adverse effects.**
- **Oral contraceptives reduce Its serum concentrations because of induction of glucuronidation by ethinyl estradiol.**

Clinical Considerations with Specific Drugs

Important Adverse Reactions:

A. Concentration-dependent:

- **Diplopia, dizziness,, unsteadiness, headache.**

B. Idiosyncratic:

- **Generalized eryhthematous and morbilliform rash, Steven-Johnson syndrome, which may necessitate withdrawal.**

Clinical Considerations with Specific Drugs

Topiramate

Mechanism of Action:

- **It has multiple modes of action involving voltage-dependent Na^+ channels, $GABA_A$-receptor subunits, high-voltage Ca^{2+} channels, and kainate/α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) subunits.**
- **It also inhibits carbonic anhydrase, which may have some antiseizure effects.**

Clinical Considerations with Specific Drugs

Place in Therapy:

- **It is used as monotherapy or adjunctive therapy for focal onset seizures is patients 2 years or older.**
- **It is also used for tonic–clonic seizures in primary generalized epilepsy and generalized seizures in patients with LGS.**
- **It has benefit in patients with co-morbidities (migraines, obesity).**

Clinical Considerations with Specific Drugs

Drug Interactions:

- It increases phenytoin serum concentrations due to inhibition of CYP2C19.
- It may increase the clearance of valproic acid and the formation of its toxic metabolites.
- It increases the clearance of ethinyl estradiol at doses higher than 200 mg/day.
- Dose should be adjusted in renal impairment.
- Metabolism is increased 50% when given with enzyme-inducing ASDs.

Clinical Considerations with Specific Drugs

Important Adverse Reactions:

A. Concentration-dependent:

- **Difficulty concentrating, psychomotor slowing, speech or language problems, somnolence, fatigue, dizziness, headache.**

B. Idiosyncratic:

- **Metabolic acidosis, acute glaucoma, oligohydrosis (deficient sweating).**

C. Chronic:

- **Kidney stones, weight loss.**

Clinical Considerations with Specific Drugs

Gabapentin:

Mechanism of Action:

- **It elevates human brain GABA levels.**
- **It binds to the α2δ subunit of Ca^{2+} channels which may explain its analgesic effects.**

Place in Therapy:

- **It is used for focal-onset seizures with or without secondary generalization in patients 3 years and older.**
- **It is useful in treating epilepsies with neuropathic pain.**

Clinical Considerations with Specific Drugs

Drug Interactions:

- Cimetidine reduce clearance by 10%.
- Bioavailability is reduced 20% by aluminum antacids.

Important Adverse Effects:

A. Concentration-dependent:

- Dizziness, somnolence, fatigue, ataxia.

B. Idiosyncratic:

- Pedal edema

D. Chronic:

- Weight gain.

Clinical Considerations with Specific Drugs

Levetiracetam:

Mechanism of Action:

- **It binds to synaptic vesicle protein SV2A, in presynaptic terminals and inhibits neurotransmitter release.**

Place in Therapy:

- **Adjunctive therapy in focal-onset seizures in patients 12 years of age or older, myoclonic seizures, and primary generalized seizures.**

Clinical Considerations with Specific Drugs

Pharmacokinetics:

- **Renal elimination mainly (66%).**
- **Dose should be reduced by 50% in severe liver cirrhosis.**
- **It is significantly excreted into breast milk.**

Important Adverse Effects:

A. Concentration-dependent:

- **Sedation, behavioral disturbances.**

B. Idiosyncratic:

- **Psychosis.**

Clinical Considerations with Specific Drugs

Zonisamide:

Mechanism of Action:

- It inhibits slow Na^+ channels and T-type Ca^{2+} channels , and possibly glutamate release.
- It has a weak carbonic anhydrase inhibitory effect.

Place in Therapy:

- It is used for the adjunctive treatment of focal-onset seizures and may be considered first-line.

Pharmacokinetics:

- It crosses the placenta, and the concentration in breast milk is similar to that in the plasma.

Clinical Considerations with Specific Drugs

Important Adverse Effects:

A. Concentration-dependent:

- **Dizziness, sedation, cognitive impairment, nausea.**

B. Idiosyncratic:

- **Rash, metabolic acidosis, oligohydrosis**

D. Chronic:

- **Kidney stones, weight loss.**

Therapy of Diabetes Mellitus

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Therapy of Diabetes Mellitus

- **Diabetes mellitus (DM) is a heterogeneous group of metabolic disorders characterized by hyperglycemia.**
- **It is associated with abnormalities in carbohydrate, fat, and protein metabolism.**
- **It may result in chronic complications including microvascular, macrovascular, and neuropathic disorders.**

Therapy of Diabetes Mellitus

- **DM is the leading cause of blindness and end-stage renal disease.**
- **It may result in lower extremity amputations, and cardiovascular events.**

TABLE 30-2 Type 1 and Type 2 Diabetes Mellitus

	TYPE 1	TYPE 2
Etiology	Autoimmune destruction of pancreatic β-cells	Insulin resistance, with inadequate β-cell function to compensate
Insulin levels	Absent or negligible	Typically higher than normal
Insulin action	Absent or negligible	Decreased
Insulin resistance	Not part of syndrome but may be present (e.g., in obese patients)	Yes
Age of onset	Typically <30 years	Typically >40 years
Acute complications	Ketoacidosis Wasting	Hyperglycemia (can lead to hyperosmotic seizures and coma)
Chronic complications	Neuropathy Retinopathy Nephropathy Peripheral vascular disease Coronary artery disease	Same as type 1
Pharmacologic interventions	Insulin	A number of drug classes are available, including insulin if other therapies fail

Type 1 and type 2 diabetes mellitus are both associated with increased blood glucose levels, but the two diseases result from distinct pathophysiologic pathways. In type 1 diabetes mellitus, there is an absolute lack of insulin secondary to autoimmune destruction of pancreatic β-cells. The etiology of type 2 diabetes is less well understood but seems to involve impaired insulin sensitivity and an inadequate level of compensatory insulin production by pancreatic β-cells. Although type 1 and type 2 diabetes have different acute complications (*see text*), they share similar chronic complications. Insulin is the primary pharmacologic intervention for type 1 diabetes, while type 2 diabetes can be treated with a number of different agents.

Drug-induced Diabetes Mellitus

1. **Pyriminil (vacor) (rodenticide) – loss of pancreatic β-cells.**
2. **Pentamidine – cytotoxic effect on pancreatic β-cells (type 1).**
3. **Nicotinic acid – impairment of insulin action.**
4. **Glucocorticoids – Metabolic effects and insulin antagonism.**
5. **Thyroid hormones – increase hepatic glucose production.**
6. **Growth hormone - reduces insulin sensitivity resulting in mild hyperinsulinemia, and increased blood glucose levels**
7. **Diazoxide: inhibition of insulin secretion.**

Drug-induced Diabetes Mellitus

8. β-adrenergic agonists – glycogenolysis, and gluconeogenesis.
9. Thiazides – hypokalemia-induced inhibition of insulin release.
10. Phenytoin – induces insulin insensitivity.
11. Interferone – β-cell destruction (type 1)
12. Chronic alcoholism - insulin resistance and pancreatic β-cell dysfunction.
13. Cyclosporine – suppresses insulin production and release.

Drug-induced Diabetes Mellitus

14. **HIV protease inhibitors - insulin resistance with insulin deficiency relative to hyper-glucagonemia.**
15. **Atypical antipsychotics (clozapine and olanzapine) – weight gain and insulin resistance.**
16. **Megestrol acetate – insulin resistance.**
17. **Others …**

Therapy of Diabetes Mellitus

Desired Outcome:

The primary goals of DM management are:

1. **To reduce the risk of microvascular and macrovascular disease complications.**
2. **To ameliorate symptoms.**
3. **To reduce mortality.**
4. **To improve quality of life.**
5. **To minimize weight gain and hypoglycemia.**

Therapy of Diabetes Mellitus

- **Early diagnosis and treatment to near-normoglycemia reduces the risk of developing microvascular (retinopathy, nephropathy, and neuropathy) disease complications.**

Therapy of Diabetes Mellitus

- **Aggressive management of cardiovascular risk factors: smoking cessation, treatment of dyslipidemia, intensive blood pressure control, and antiplatelet therapy are needed to reduce the risk of developing macrovascular disease (ischemic heart disease, peripheral vascular disease, and cerebrovascular disease).**

Therapy of Diabetes Mellitus

- **Hyperglycemia also contributes to poor wound healing by compromising white blood cell function and altering capillary function.**
- **Diabetic ketoacidosis (DKA) and hyperosmolar hyperglycemic state (HHS) are severe manifestations of poor diabetes control, always requiring hospitalization.**

Non-pharmacologic Management

1. **Screening (for the presence of DM).**
2. **Monitor for:**

- **blood glucose, HbA_{1c}, fasting lipid profile, urinary albumin (urine albumin-to-creatinine ratio [UACR]) and glomerular filtration rate (GFR), diabetic neuropathy, and dilated eye examination.**

Non-pharmacologic Management

3. **Glycemic goals:**

- **HbA_{1c} goal for non-pregnant adults of <7%, or of <6.5% without significant hypoglycemia.**
- **Critically ill (Hospital) glucose: 140-180 mg/dL, or more strict guidelines down to 110-140 mg/dL (without hypoglycemia).**
- **(*The above percentages may differ depending on the method of HbA_{1c} measurement*).**

Non-pharmacologic Management

5. **Medical nutrition therapy:**

- **Weight loss is recommended for all insulin-resistant/ overweight or obese individuals.**

a) **Either low-carbohydrate, low-fat, calorie-restricted diets, or Mediterranean diets.**

b) **Healthier eating behaviors leading to sustained weight loss over time is more important than a specific diet.**

Non-pharmacologic Management

- **In individuals with type 2 diabetes, ingested protein appears to increase insulin response without increasing plasma glucose concentrations.**
- **Therefore, carbohydrate sources high in protein should NOT be used to treat or prevent hypoglycemia.**
- **Saturated fat should be <7% of total calories.**

Non-pharmacologic Management

- **A Mediterranean-style eating pattern, rich in monounsaturated fatty acids (olive oil), may benefit glycemic control and reduce CVD risk factors.**
- **Consider financial and cultural food issues.**
- **Discourage bedtime and between-meal snacks, and set realistic goals.**

Non-pharmacologic Management

- **A diet low in fat is recommended for patients with CVD.**
- **Avoid a high-protein diet in patients with nephropathy.**
- **Supplement with all of the essential vitamins and minerals.**

Non-pharmacologic Management

6. **Physical Activity:**

- **Aerobic exercise improves insulin sensitivity, modestly improves glycemic control, reduces cardiovascular risk, contributes to weight loss or maintenance, raises HDH-cholesterol and improves well-being.**
- **Physical activity goals include at least 150 min/wk of moderate intensity exercise spread over at least 3 days/week with no more than 2 days between activities.**

Non-pharmacologic Management

- **Resistance/Strength training is recommended at least 2 times a week in patients without proliferative diabetic retinopathy, and ischemic heart disease.**

Non-pharmacologic Management

7. **Patient Education:**

- **It is NOT appropriate to give patients with DM brief instructions and a few pamphlets.**
- **Diabetes education, at initial diagnosis and at ongoing intervals over a life-time, is critical.**
- **Healthy behaviors include healthy eating, being active, monitoring, taking medication, problem solving, reducing risk, and healthy coping.**

Non-pharmacologic Management

- **The patient must be involved in the decision-making process with knowledge of the disease and associated complications.**
- **Emphasize that complications can be prevented or minimized with good glycemic control and managing risk factors for CVD.**
- **Motivational interviewing techniques to encourage patients to identify barriers that hinder achieving health goals, and then work to solve them, are essential.**

Other Recommendations

A. **Blood pressure:**

- **Systolic/diastolic blood pressure should be treated to <140 mm / <90 mm Hg.**
- **Lower goals <130 mm Hg / <80 mm Hg may be appropriate for younger patients.**
- **Life-style intervention such as weight loss, and diet including reducing sodium and increasing potassium.**
- **Initial drug therapy should be with an ACEi or an angiotensin-receptor blocker (ARB); if intolerant to one, the other should be tried.**

Other Recommendations

B. **Dyslipidemia:**

- **Lifestyle modification focusing on the reduction of saturated fat, and cholesterol intake; increasing omega-3 fatty acids intake, use of viscous fiber, and plant sterols; weight loss, and increased physical activity should be recommended.**
- **Consider the use of statins according to risks.**

Other Recommendations

C. **Antiplatelet Therapy:**

- **Use aspirin (75-162 mg daily) for <u>secondary</u> cardioprotection.**

D. **Hospitalized Patients:**

- **Critically ill: IV insulin protocol.**
- **Non-critically ill: scheduled subcutaneous insulin with basal, nutritional, and correction coverage.**

E. **Psychosocial:**

- **Assess the patient's psychological and social situation as an ongoing part of the medical management of diabetes.**

Prevention of Diabetes Mellitus

A. Efforts to prevent type 1 diabetes focused on immunomodulators and low dose insulin, but the results are not yet conclusive.

B. Prevention of type 2 diabetes:

1. The "4 life-style pillars" for the prevention of type 2 diabetes are to:

a) decrease weight.

b) increase aerobic exercise.

c) increase fiber in diet.

d) decrease fat intake.

Prevention of Diabetes Mellitus

2. **Drugs:**

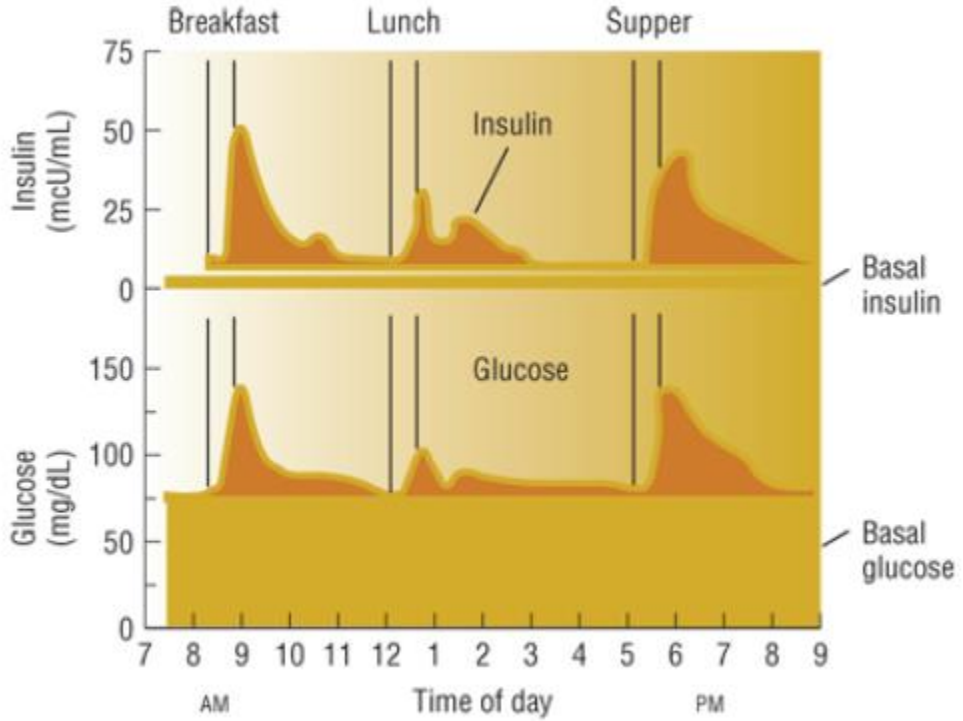
a. **Metformin therapy reduces the risk of developing type 2 DM, especially in obese, <60-year-old patients, and women with prior gestational diabetes mellitus (GDM).**

b. **Rosiglitazone reduces the incidence of type 2 diabetes.**

c. **Acarbose and liraglutide decrease progression to type 2 DM.**

Pharmacologic Therapy (Type 1 DM)

- **All patients with type 1 DM require insulin.**



Relationship between insulin and glucose over the course of a day.

Pharmacologic Therapy (Type 1 DM)

- **Attempt to mimic normal secretion of insulin.**
- **One or two injections of insulin daily will in NO way mimic normal physiology, and therefore, is unacceptable.**
- **The timing of insulin onset, peak, and duration of effect must match meal patterns and exercise schedules to achieve adequate blood glucose control throughout the day.**

Insulin

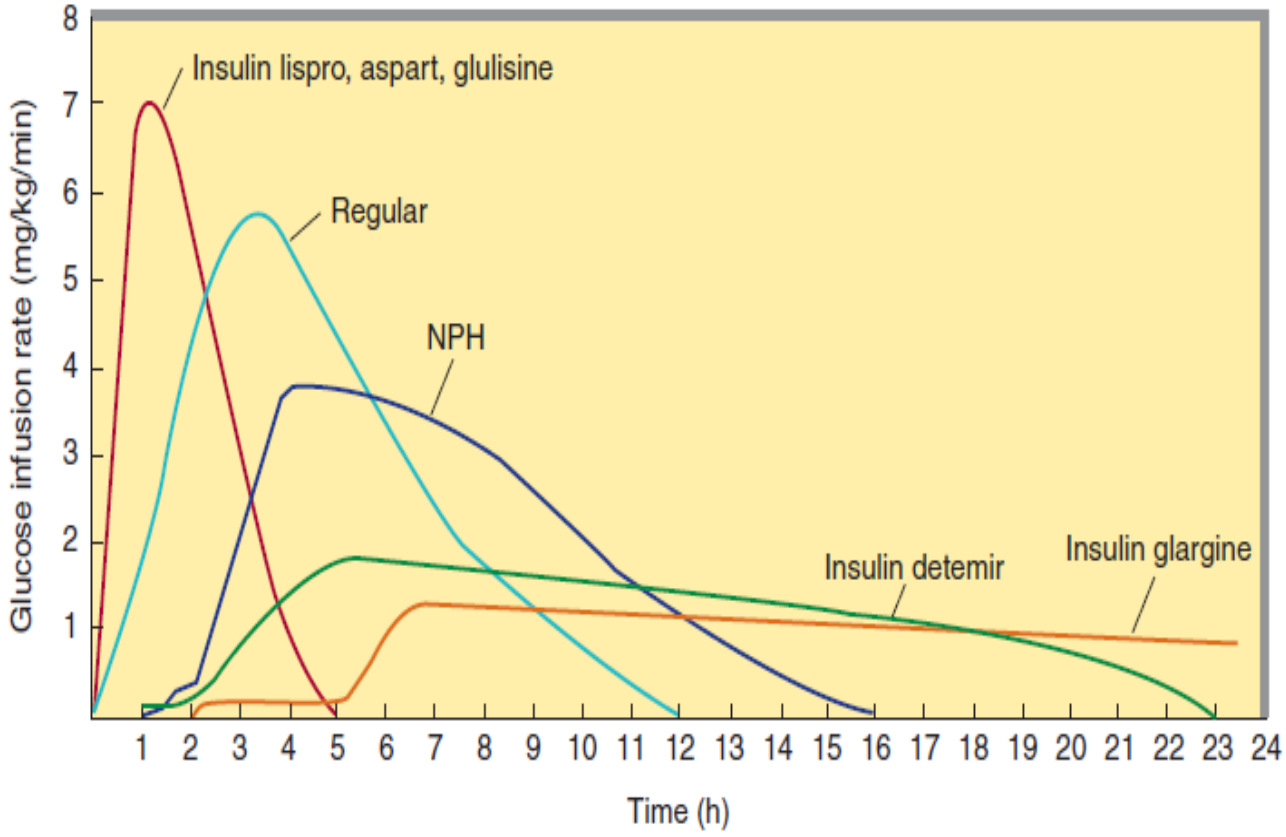


FIGURE 41–5 Extent and duration of action of various types of insulin as indicated by the glucose infusion rates (mg/kg/min) required to maintain a constant glucose concentration. The durations of action shown are typical of an average dose of 0.2–0.3 U/kg. The durations of regular and NPH insulin increase considerably when dosage is increased.

Pharmacokinetics of Select Insulins Administered Subcutaneously

Type of Insulin	Onset (Hours)	Peak (Hours)	Duration (Hours)	Maximum Duration (Hours)	Appearance
Rapid acting					
Aspart	15-30 min	1-2	3-5	5-6	Clear
Lispro	15-30 min	1-2	3-4	4-6	Clear
Glulisine	15-30 min	1-2	3-4	5-6	Clear
Technosphere[a]	5-10 min	0.75-1	~3	~3	Powder
Short-acting					
Regular	0.5-1.0	2-3	4-6	6-8	Clear
Intermediate acting					
NPH	2-4	4-8	8-12	14-18	Cloudy
Long acting					
Detemir	~2 hours	__[b]	14-24	20-24	Clear
Glargine (U-100)	~2-3 hours	__[b]	22-24	24	Clear
Degludec	~2 hours	__[b]	30-36	36	Clear
Glargine (U-300)	~2 hours	__[b]	24-30	30	Clear

[a]Technosphere insulin is inhaled.

[b]Glargine is considered "flat" though there may be a slight peak in effect at 8-12 hours, and with detemir at ~8 hours, but both have exhibited peak effects during comparative testing, and these peak effects may necessitate changing therapy in a minority of type 1 DM patients. Degludec and U-300 insulin glargine appears to have less peak effect compared to U-100 insulin glargine.

Intensive Insulin Regimens

	7 am meal	11 am meal	5 pm meal	Bed time
2 doses (R or rapid acting) + N	R, L, A, Glu + N		R, L, A, Glu + N	
3 doses (R or rapid acting) + N	R, L, A, Glu + N	R, L, A, Glu	R, L, A, Glu + N	
4 doses (R or rapid acting) + N	R, L, A, Glu	R, L, A, Glu	R, L, A, Glu	N
4 doses (R or rapid acting) + N	R, L, A, Glu + N	R, L, A, Glu	R, L, A, Glu	N
4 doses (R or rapid acting) + long acting	R, L, A, Glu	R, L, A, Glu	R, L, A, Glu	G or D
CS-II pump	Adjusted basal + Bolus	Adjusted basal + Bolus	Adjusted basal + Bolus	
3 prandial doses	P added to previous regimens	P added to previous regimens	P added to previous regimens	

A, aspart; CS-II, continuous subcutaneous insulin infusion; D, detemir or degludec; G, glargine; GLU, glulisine; L, lispro; N, NPH; P, pramlintide; R, regular.

Pharmacologic Therapy (Type 1 DM)

- **The simplest regimens that can approximate physiologic insulin release use "split-mixed" injections consisting of a morning dose of an intermediate-acting insulin (NPH) and a "bolus" rapid-acting insulin or regular insulin prior to the morning and evening meals.**
- **The morning intermediate-acting insulin dose provides basal insulin during the day and provides "prandial" coverage for the midday meal.**

Pharmacologic Therapy (Type 1 DM)

- **The evening intermediate-acting insulin dose provides basal insulin throughout the evening and overnight.**
- **That is acceptable when patients have fixed timing of meals and carbohydrate intake.**
- **However, This regimen may NOT achieve good glycemic control overnight without causing nocturnal hypoglycemia.**
- **Moving the evening NPH dose to bedtime may improve glycemic control and reduce the risk of nocturnal hypoglycemia.**

Pharmacologic Therapy (Type 1 DM)

- **“Basal-bolus” regimens using multiple daily injections (MDIs) may mimic normal insulin physiology, with a combination of intermediate- or long-acting insulin to provide the basal insulin, and a rapid-acting insulin to provide prandial coverage.**
- **Long-acting insulins include insulin detemir, glargine, or degludec.**

Pharmacologic Therapy (Type 1 DM)

- **Bolus or prandial insulin can be provided by either regular insulin or rapid-acting insulin analogs: lispro, aspart, or glulisine.**
- **The rapid onset and short duration of action of the rapid-acting insulin analogs more closely replicate normal physiology than does regular insulin.**
- **(Remember that regular insulin is soluble or crystalline zink insulin).**

Pharmacologic Therapy (Type 1 DM)

- **Approximately 50% of total daily insulin replacement should be in the form of basal insulin and the other 50% in the form of bolus insulin, divided between meals.**
- **In new patients, the initial total daily dose is usually between 0.5 and 0.6 units/kg/day.**

Pharmacologic Therapy (Type 1 DM)

- **Continuous subcutaneous insulin infusion (CS-II) or insulin pumps using a rapid-acting insulin is the most sophisticated and precise method for insulin delivery. In highly motivated patients, it achieves excellent glycemic control more than MDI.**
- **Insulin pump therapy may also be paired to continuous glucose monitoring (CGM), which allows calculation of a correct insulin dose, as well as alert the patient to hypoglycemia and hyperglycemia.**

Pharmacologic Therapy (Type 1 DM)

- **Insulin pumps require greater attention to details and more frequent self-monitored blood glucose (SMBG) than does a basal-bolus MDI regimen.**
- **Patients need extensive training on how to use and maintain their pump.**

Pharmacologic Therapy (Type 1 DM)

- **All patients treated with insulin should be instructed how to recognize and treat hypoglycemia.**
- **At each visit, patients with type 1 DM should be evaluated for hypoglycemia including the frequency and severity of hypoglycemic episodes.**

Pharmacologic Therapy (Type 1 DM)

- Hypoglycemic unawareness may result from autonomic neuropathy or from frequent episodes of hypoglycemia.
- The loss of warning signs of hypoglycemia is a relative contraindication to continued intensive therapy.

Pharmacologic Therapy (Type 1 DM)

- **Patients who have erratic postprandial glycemic control despite proper insulin dose may benefit from addition of the amylinomimetic pramlintide.**
- **Amylin suppresses endogenous production of glucose in the liver.**
- **Pramlintide taken prior to each meal can improve postprandial blood glucose control.**
- **It is NOT a substitute for bolus insulin.**

Pharmacologic Therapy (Type 1 DM)

- **Pramlintide can NOT be mixed with insulin requiring the patient to take an additional injection at each meal.**
- **When pramlintide is initiated, the dose of prandial insulin should be reduced by 30 - 50%, to prevent hypoglycemia.**

Pharmacologic Therapy (Type 1 DM)

Pramlintide:

1. **Slows gastric emptying – mediated by the vagus nerve.**
2. **Reduces glucagon secretion.**
3. **Promotes satiety or reduce appetite - centrally.**
4. **Produces moderate weight loss.**

- **Main adverse effects include: Hypoglycemia and GIT disturbances (nausea & vomiting), and anorexia).**

Pharmacologic Therapy (Type 2 DM)

1. Symptomatic patients may initially require treatment with insulin or combination therapy.
2. All patients are treated with therapeutic life-style modification.
3. Patients with HbA_{1c} of 7.5% or less are usually treated with metformin (which is unlikely to cause hypoglycemia).
4. Those with HbA_{1c} > 7.5% but < 8.5% could be initially treated with a single agent, or combination therapy.

Pharmacologic Therapy (Type 2 DM)

5. **Patients with higher initial HbA_{1c} will require two agents OR insulin.**
6. **All therapeutic decisions should consider the needs and preferences of the patient, if medically possible.**
7. **Obese patients without contraindications are often started on metformin which is titrated up to 2,000 mg/day.**

Pharmacologic Therapy (Type 2 DM)

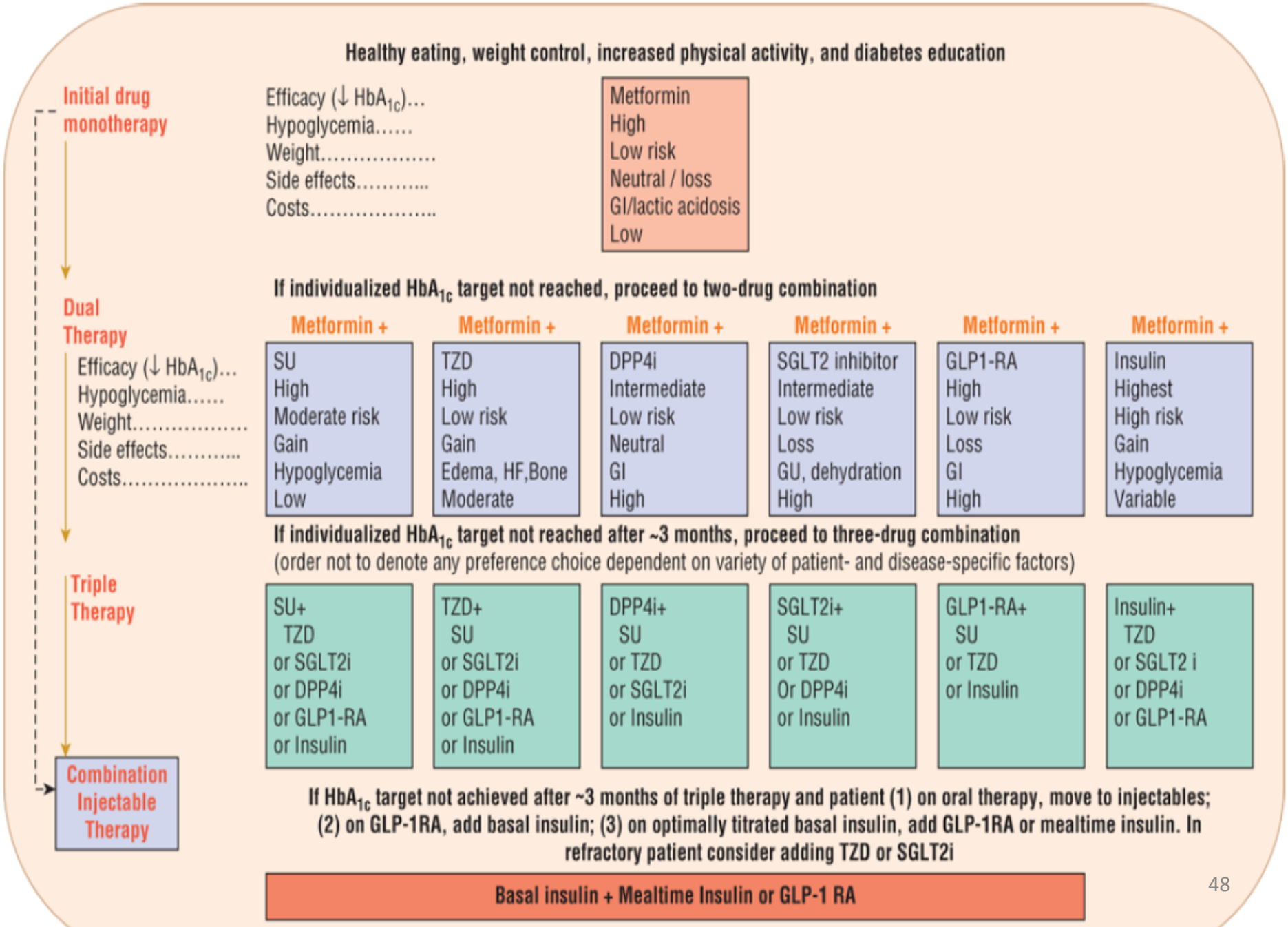
8. **Non-obese patients are more likely to be insulinopenic, necessitating medications that may increase insulin secretion.**
9. **An insulin secretagogue, such as a sulfonylurea, is often added second.**

- **Sulfonylureas have several potential drawbacks including weight gain and hypoglycemia.**
- **They do NOT produce a durable glycemic response.**

Pharmacologic Therapy (Type 2 DM)

10. Better choices include Dipeptidyl peptidase-4 inhibitors (DPP-4 inhibitors) and GLP-1 receptor agonist but they have therapeutic and safety limitations.
11. Thiazolidinediones (TZDs) produce a more durable glycemic response and are unlikely to cause hypoglycemia, but weight gain, fluid retention and the risk of new onset heart failure have limited their use.

Antihyperglycemic Therapy Recommendations in Type 2 Diabetes. General Recommendations. *(Data from reference 20.)*



Drug & class	Dose (mg)	Duration of action (hours)	Drug	Dose (mg)	Duration of action (hours)
Sulfonylureas					
Glimepiride	1-8	24	Glipizide	2.5-40	12-24
Glyburide	1.25-20	12-24	Glipizide extended release	5-20	24
Micronized glyburide	1-12	24			
Non-sulfonyureas secretagogues					
Rapaglinide	0.5-4	2-3	Nateglinide	60-120	2-4
Biguanides					
Metformin	500-2500	6-12	Metformin extended release	1500-2000	24
Thiazolidinediones					
Rosiglitazone	4-8	Poorly correlated with half-life. Max effect ~ 4 weeks	Poiglitazone	15-45	Poorly correlated with half-life. Max effect ~ 4 weeks
α-glucosidae inhibitors					
Acarbose	25-50	Affects absorption of carbohydrates in a single meal	Miglitol	25-100	Affects absorption of carbohydrates in a single meal
GLP-1 receptor agonists / Incretin mimetics					
Exenatide	5-10 mcg	10	Liraglutide	0.6-1.8	24
DPP-4 inhibitors					
Sitagliptin	100	24	Saxagliptin	2.5-5	24
Linagliptin	5	24			
Amylin mimetics					
Pramlintide	15-60 (type 1 DM) 60 or 120 (type 2 DM)	C_{max} 20 min			
Bile acid sequestrants					
Colesevelam	3750	N/A			

Pharmacologic Therapy (Type 2 DM)

Treatment selection should be based on multiple factors:

1. **A patient who has had diabetes for several years, due to progressive failure of β-cell function, is more likely to require insulin therapy.**
2. **If the patient has multiple co-morbidities (CVD, dementia, depression, osteoporosis, heart failure, recurrent genitourinary (GU) infections, some medications may be poor choices based on their potential adverse effects.**

Pharmacologic Therapy (Type 2 DM)

3. **If the patient's postprandial blood glucose readings are the primary reason for poor control, pick a medication that addresses postprandial blood glucose fluctuations.**
4. **If the patient's fasting blood glucose readings are consistently elevated, a medication that addresses fasting blood glucose would be a better choice.**

Pharmacologic Therapy (Type 2 DM)

5. **Adverse effect profile, contraindications, hypoglycemia potential, and tolerability by the patient, should be considered when selecting therapy.**
6. **Motivation, resources, and potential difficulties with adherence should also influence treatment selection.**

Pharmacologic Therapy (Type 2 DM)

7. If the patient is an older adult, the risk of hypoglycemia and other adverse effects increases and life expectancy diminishes. These factors should influence medication choices and HbA1c goals.
8. Non-glycemic effects (CVD reduction with medications, lipid effects, blood pressure effects, weight, and durability of HbA_{1c} reduction) may all influence the decision.

Pharmacologic Therapy (Type 2 DM)

9. **It is unlikely that any one drug class will arrest β-cell failure, necessitating combination therapy.**

- **The combination of a TZD and GLP-1 receptor agonist is a good one:**

a) **TZDs reduce apoptosis of β-cells.**

b) **GLP-1 receptor agonists augment pancreatic function.**

- **Metformin, pioglitazone, and exenatide are promising.**

Glucagon-like peptide-1 (GLP-1) from the GIT

1. It enhances insulin release in response to an ingested meal.
2. It suppresses glucagon secretion.
3. It delays gastric emptying.
4. It decreases appetite.
5. It is degraded by dipeptidyl peptidase-4 (DPP-4).

Pharmacologic Therapy (Type 2 DM)

Exenatide:

- **It is a long-acting analogue of GLP-1, Acts as agonist at GLP-1 receptors.**
- **Used as adjunctive therapy in patients with type 2 diabetes treated with metformin, or metformin plus sulfonylureas who still have suboptimal glycemic control.**
- **Delays gastric emptying.**
- **Suppresses postprandial glucagon release.**

Pharmacologic Therapy (Type 2 DM)

- It increases insulin secretion in a glucose-dependent manner. The increased insulin secretion is speculated to be due in part to:

a) an increase in beta-cell mass, from decreased beta-cell apoptosis.

b) increased beta-cell formation.

c) or both. (Noticed in culture)

- Suppresses appetite.
- Associated with weight loss.

Pharmacologic Therapy (Type 2 DM)

Adverse effects:

1. **Nausea, vomiting, diarrhea: major adverse effect is nausea (45%), which is dose-dependent and declines with time.**
2. **Acute pancreatitis.**
3. **Renal impairment and acute renal injury.**

- **Not associated with hypoglycemia unless used in combination.**

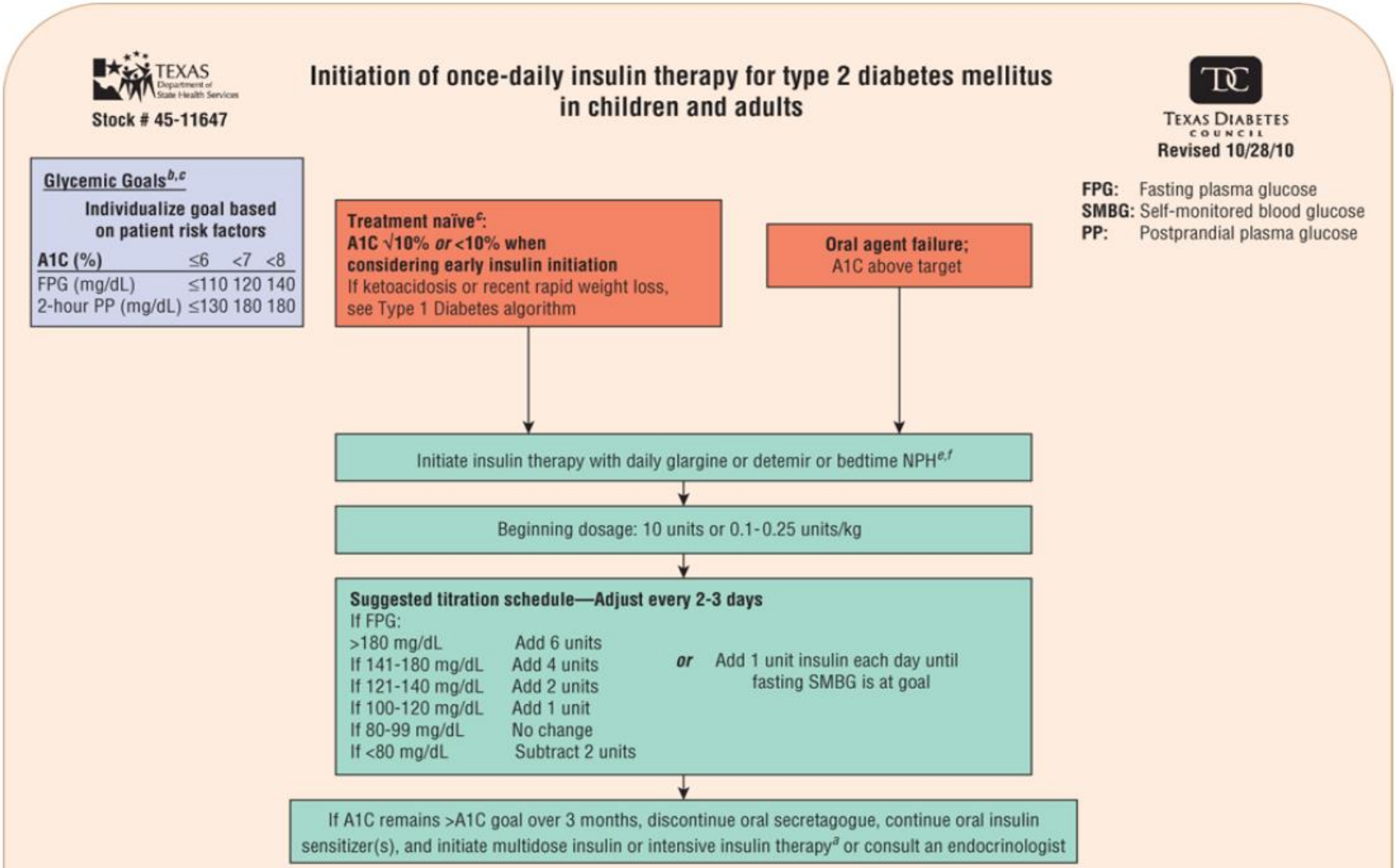
Pharmacologic Therapy (Type 2 DM)

- **With time some patients with type 2 DM become relatively insulinopenic necessitating insulin therapy.**
- **In these patients use insulin injections at bedtime (intermediate- or long-acting basal insulin) while continuing to use oral agents or GLP-1 receptor agonists for control during the day.**

Pharmacologic Therapy (Type 2 DM)

- **This strategy is associated with less weight gain, equal efficacy, and lower risk of hypoglycemia when compared to starting prandial insulin or split-mix twice daily insulin regimens.**
- ***Any modification of this strategy should depend on fasting and posprandial glucose monitoring, HbA_{1c} monitoring, and times of development of hypoglycemia.***

Simplified Insulin algorithm for type 2 DM in children and adults. See: www.texasdiabetescouncil.org for current algorithms. *(Reprinted from the Texas Diabetes Council.)*



The SI equivalents for A1C from the figure are: 4% (0.04; 20 mmol/mol Hb), 6% (0.06; 42 mmol/mol Hb), 7% (0.07; 53 mmol/mol Hb), 8% (0.08; 64 mmol/mol Hb), 10% (0.10; 86 mmol/mol Hb), and 1% change (0.01; 11 mmol/mol Hb).

The SI equivalents for glucose from the figure are: 80 mg/dL (4.4 mmol/L), 99 mg/dL (5.5 mmol/L), 100 mg/dL (5.6 mmol/L), 110 mg/dL (6.1 mmol/L), 120, and 121 mg/dL (6.7 mmol/L), 130 mg/dL (7.2 mmol/L), 140 and 141 mg/dL (7.8 mmol/L), 180 mg/dL (10 mmol/L).

Comparative Pharmacology of Antidiabetic Agents

Agent/Generic Name (Brand Name)/Mechanism	FDA Indications	A1C Efficacy[a]	Adverse Effects	Comments
Insulin Replaces or augments endogenous insulin	Monotherapy; combined with any oral agent	↓ A1C[b] ↓FPG[b] ↓ PPG[b] ↓ TG	Hypoglycemia, weight gain, lipodystrophy, local skin reactions	Offers flexible dosing to match lifestyle and glucose concentrations. Rapid onset. Safe in pregnancy, renal failure, and liver dysfunction. Drug of choice when patients do not respond to other antidiabetic agents.
Insulin-Augmenting Agents				
Nonsulfonylurea secretagogues (glinides) Repaglinide (Prandin) Nateglinide (Starlix) Stimulates insulin secretion	Monotherapy; combined with metformin or TZD	Monotherapy: ↓ A1C ~1% (repaglinide) ↓ A1C ~0.5% (nateglinide) Combination: additional 1% ↓ A1C	Hypoglycemia, weight gain	Take only with meals. If a meal is skipped, skip a dose. Flexible dosing with lifestyle. Safe in renal and liver failure. Rapid onset. Useful to lower PPG.
Sulfonylureas Various; see Table 53-28. Stimulates insulin secretion. May decrease hepatic glucose output and enhance peripheral glucose utilization.	Monotherapy; combined with metformin; combined with insulin (glimepiride)	Monotherapy: ↓ A1C ~1% Combination: additional 1% ↓ in A1C	Hypoglycemia, especially long-acting agents; weight gain (5–10 pounds); rash, hepatotoxicity, alcohol intolerance, and hyponatremia rare	Very effective agents. Some can be dosed once daily. Rapid onset of effect (1 week).

Incretin-Based Therapies

Glucagonlike peptide-1 receptor agonists/incretin mimetic Exenatide (Byetta) Liraglutide (Victoza) Stimulates insulin secretion, delays gastric emptying, reduces postprandial glucagon levels, improved satiety	Monotherapy (exenatide only) Combined with metformin, SFU, or TZD, combined with metformin + SFU; combined with metformin + TZD	Monotherapy: ↓ A1C 0.8%–0.9% Combination: additional 1% ↓ in A1C	GI: nausea, vomiting, diarrhea; hypoglycemia (with SFUs); weight loss; reports of acute pancreatitis	Weight loss. Exenatide: take within 60 minutes before morning and evening meals or before two main meals of the day (≥6 hours apart). Liraglutide: Do not use if personal or family history of medullary thyroid carcinoma or in patients with multiple endocrine neoplasia syndrome type 2. Do not use in patients with gastroparesis or severe GI disease. Administered by SC injection; pen device in use does not need to be refrigerated. Rare cases of pancreatitis with both drugs.
DPP-4 inhibitors Sitagliptin (Januvia) Saxagliptin (Onglyza) Linagliptin (Tradjenta) Stimulates insulin secretion and reduces postprandial glucagon levels	Monotherapy; combined with metformin, SFU, or TZD; insulin (sitagliptin only)	Monotherapy: ↓ A1C 0.5%–0.8% Combination: ↓ A1C 0.5%–0.9%	Headache, nasopharyngitis, hypoglycemia (with SFU), rash (rare)	Dosed once daily. Taken with or without food. No weight gain or nausea. Need to adjust sitagliptin and sazagliptin dose in renal dysfunction. Reduce dose of SFU when combined. Rare reports of pancreatitis.

Amylin Receptor Agonists

Amylin mimetic Pramlintide (Symlin)	Type 1: Adjunct to mealtime insulin	T1: ↓ A1C 0.33% T2: ↓ A1C 0.40%	GI: nausea, decreased appetite	Take only immediately before meals; administered by SC injection. Do not use in patients with gastroparesis.
Stimulates insulin secretion, delays gastric emptying, reduces postprandial glucagon levels, improved satiety	Type 2: Adjunct to mealtime insulin; ± SFU and metformin		Headache; hypoglycemia; weight loss (mild)	

Insulin Sensitizers

Insulin Sensitizers

Biguanides Metformin (Glucophage) ↓ Hepatic glucose output; ↑ peripheral glucose uptake	Monotherapy; combined with SFU or TZD; or with insulin	Monotherapy: ↓ A1C ~1% Combination: additional 1% ↓ in A1C	GI: nausea, cramping, diarrhea; lactic acidosis (rare)	Titrate dose slowly to minimize GI effects. No hypoglycemia or weight gain; weight loss possible. Mild reduction in cholesterol. Do not use in patients with renal or severe hepatic dysfunction.
Thiazolidinediones Rosiglitazone (Avandia) Pioglitazone (Actos) Enhances insulin action in periphery; increases glucose utilization by muscle and fat tissue; decreases hepatic glucose output	Monotherapy; combined with SFU, TZD, or insulin; combined with SFU + TZD	Monotherapy: ↓ A1C ~1% Combination: additional 1% ↓ in A1C	Mild anemia; fluid retention and edema, weight gain, macular edema, fractures (in women)	Can cause or exacerbate HF; do not use in patients with symptomatic HF or class III or IV HF. Rosiglitazone may increase risk of MI. Increased risk of distal fractures in older women. Pioglitazone may increase risk of bladder cancer when used for >1 year. Slight reduction in TG with pioglitazone; slight increase in LDL-C with rosiglitazone. LFTs must be measured at baseline and periodically thereafter. Slow onset (2–4 weeks).

Delayers of Carbohydrate Absorption

α-Glucosidase inhibitors Acarbose (Precose) Miglitol (Glyset) Slow absorption of complex carbohydrates	Monotherapy; combined with SFUs, metformin, or insulin	Monotherapy: ↓ A1C ~0.5% Combination: additional ~0.5% ↓ A1C	GI: flatulence, diarrhea. Elevations in LFTs seen in doses >50 mg TID of acarbose	Useful for PPG control (↓ PPG 25–50 mg/dL). LFTs should be monitored every 3 months during the first year of therapy and periodically thereafter. Because miglitol is not metabolized, monitoring of LFTs is not required. Titrate dose slowly to minimize GI effects. No hypoglycemia or weight gain. If used in combination with hypoglycemic agents, advise patients to treat hypoglycemia with glucose tablets because absorption is not inhibited as with sucrose.
Bile acid sequestrant Colesevelam (Welchol)	Combined with metformin, SFU, or insulin	↓ A1C 0.3%–0.4%	Constipation, dyspepsia, and nausea; ↑ TG	Added benefit of ↓ LDL-C (by 12%–16%). Administer certain drugs 4 hours before. Take with a meal and liquid.

[a]Comparative effectiveness data provided for SFUs, glinides, TZDs, and α-glucosidase inhibitors.[307]

[b]Theoretically, unlimited glucose lowering with insulin therapy.

A1C, glycosylated hemoglobin; DPP-4, dipeptidyl peptidase-4; FDA, Food and Drug Administration; FPG, fasting plasma glucose; GI, gastrointestinal; HF, heart failure; LDL-C, low-density lipoprotein cholesterol; LFTs, liver function tests; MI, myocardial infarction; PPG, postprandial glucose; SC, subcutaneously; SFU, sulfonylureas; TG, triglycerides; TID, three times a day; T1, type 1 diabetes; T2, type 2 diabetes; TZD, thiazolidinediones.

Effect of Some Antidiabetics on Body Weight

Drug	Effect on body weight
Insulin	Weight gain
Sulfonylureas	Weight gain
Meglitinides	Weight gain
Metformin	No change or reduce
Thiazolidinediones	Weight gain + fluid retention
Amylin Analogues -pramlintide	Moderate weight loss
GLP-1 analogues (exenatide)	Weight loss
DPP-4 inhibitors (sitagliptin)	Weight neutral

Special Populations (Children and Adolescents with Type 2 DM)

- **Type 2 DM is increasing in adolescence probably caused by obesity and physical inactivity.**
- **Need extraordinary efforts on life-style modification measures.**
- **If failed, use metformin, sulfonylureas (or TZDs) or any combination of these that may improve glycemic control.**

Special Populations (Children and Adolescents with Type 2 DM)

- **Insulin therapy is the standard of care when glycemic goals can NOT be achieved or maintained with metformin and sulfonylurea.**

Special Populations (Elderly patients with Type 2 DM)

- Consideration of the risks of hypoglycemia, the extent of co-morbidities, self-care, nutritional status, social support, falls risk, mental status, and life expectancy should all influence glycemic goals and treatment selection.
- Avoidance of both hypo- and hyperglycemia is extremely important.

Special Populations (Elderly patients with Type 2 DM)

- **Elderly patients may have an altered presentation of hypoglycemia because of loss of autonomic nerve function with age.**
- **DPP-4 inhibitors (Sitagliptin), shorter-acting insulin secretagogues (rapaglinide), low-dose sulfonylureas, or α-glucosidase inhibitors may be used.**

Special Populations (Elderly patients with Type 2 DM)

- DPP-4 inhibitors or α-glucosidase have low risk of hypoglycemia.
- Metformin may be used at low doses if Cl_{cr} is > 30 mL/min/1.73 m^2.
- Simple insulin regimens with daily basal insulin may be appropriate.

Dipeptidyl peptidase-4 (DPP-4) inhibitors (Sitagliptin)

- **Inhibit DPP-4, the enzyme that degrades incretin hormones.**
- **Prolong the half-life of endogenous GLP-1.**
- **Decrease postprandial glucose levels.**
- **Decrease glucagon concentration.**
- **Increase circulating GLP-1 and glucose-dependent insulinotropic polypeptide (GIP) and thus, insulin concentrations in a glucose-dependent manner.**

Sitagliptin

- **Most commonly used in combination with a TZD or metformin, or sulfonylureas.**
- **May be used as monotherapy.**
- **Used for type 2 DM orally, peaks within 1–4 hours, and has a half-life of approximately 12 hours.**
- **Dosage should be reduced in patients with impaired renal function**
- **Weight neutral.**

Sitagliptin

Adverse effects:

1. **Nasopharyngitis, upper respiratory infections, headaches**
2. **Hypoglycemia when the drug is combined with insulin secretagogues or insulin. Not associated with hypoglycemia when used alone.**
3. **Acute pancreatitis which may be fatal.**
4. **Allergic reactions.**

Diabetic Ketoacidosis and Hyperosmolar Hyperglycemic State

- These are true emergencies.
- Insulin given by continuous IV infusion (regular insulin = soluble insulin = crystaline zinc insulin) to restore the patient's metabolic status is the cornerstone of therapy.
- Pay attention to volume deficits, electrolyte disturbances, and acidosis.
- Treat the precipitating problem.

Hospitalization for Intercurrent Medical Illness

- **Patients on oral agents may need transient therapy with insulin to achieve adequate glycemic control during hospitalization.**
- **It is important to stop metformin in all patients who arrive in acute care settings as contraindications to metformin are prevalent in hospitalized patients (renal dysfunction, hypoxia..).**

Perioperative Management

- **Patients who require surgery may experience worsening of glycemia similar to those admitted to hospital for a medical illness.**
- **Acute stress increases counter-regulatory hormones.**
- **Therapy should be individualized based on the type of DM, nature of the surgical procedure, previous therapy, and metabolic control prior to the procedure.**

Perioperative Management

- **Patients on oral agents may need to be transiently switched to insulin to control blood glucose, preferably as continuous insulin infusions.**
- **Metformin should be discontinued temporarily after any major surgery until it is clear that the patient is hemodynamically stable and normal renal function is documented.**

Sodium-glucose Co-transporter 2 (SGLT2) Inhibitors

- **SGLT2 is the main transporter for glucose re-absorption in the proximal tubules (90%).**
- **Inhibitors include canagliflozin which increases urinary glucose loss.**
- **Not very effective in chronic renal dysfunction and are even contraindicated.**

(SGLT2) Inhibitors

Adverse effects:

1. **Increased incidence of genital and urinary tract infections.**
2. **Intravascular volume contraction and hypotension ← osmotic diuresis.**
3. **Increase LDL cholesterol.**
4. **Higher rates of breast cancer and bladder cancer.**

*** this class is a bad idea (in my opinion!).**

FDA Warnings & Information on SGLT2 Inhibitors

- Serious Infection Of The Genital Area
- Increased Risk Of Leg And Foot Amputations With Canagliflozin
- Strengthens Kidney Warnings
- Increased Risk Of Leg And Foot Amputations, Mostly Affecting The Toes.
- Acid In The Blood And Serious Urinary Tract Infections
- Bone Fracture Risk And New Information On Decreased Bone Mineral Density.

Reference: https://www.fda.gov/drugs/postmarket-drug-safety-information-patients-and-providers/sodium-glucose-cotransporter-2-sglt2-inhibitors

Therapy of Bronchial Asthma

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Department of Pharmacology, Faculty of Medicine

Definition of Bronchial Asthma

The Global Initiative for Asthma (GINA) provides a new practical asthma definition:

- **"Asthma is a heterogeneous disease, usually characterized by chronic airway inflammation. It is defined by the history of respiratory symptoms such as wheeze, shortness of breath, chest tightness, and cough that vary over time and in intensity, together with variable expiratory airflow limitation."**
- **This is usually a reversible process.**

Definition of Bronchial Asthma

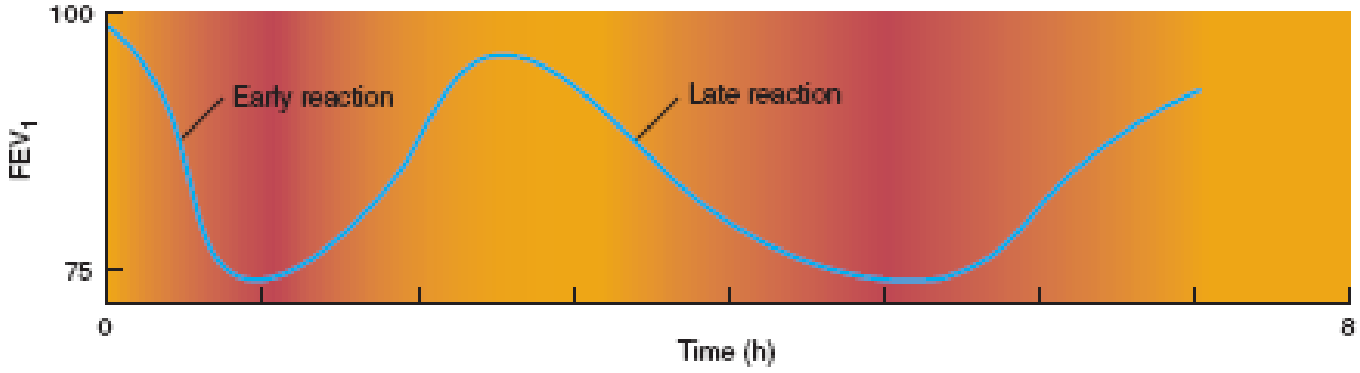
- **Airway obstruction in asthma may become irreversible, and worsen over time owing to airway remodeling.**
- **The most common cause of death from asthma is inadequate assessment of the severity of airway obstruction, and thus, inadequate therapy.**

Pathophysiology of Bronchial Asthma

- **Major characteristics of asthma include:**

1. **A variable degree of airflow obstruction (related to bronchospasm, edema, and mucous hypersecretion).**
2. **Bronchial hyper-responsiveness (BHR).**
3. **Airway inflammation.**

- **Inhaled allergen challenge in allergic patients leads to an early phase reaction that may be followed by a late-phase reaction.**


100
75
0
8
FEV_1
Early reaction
Late reaction
Time (h)

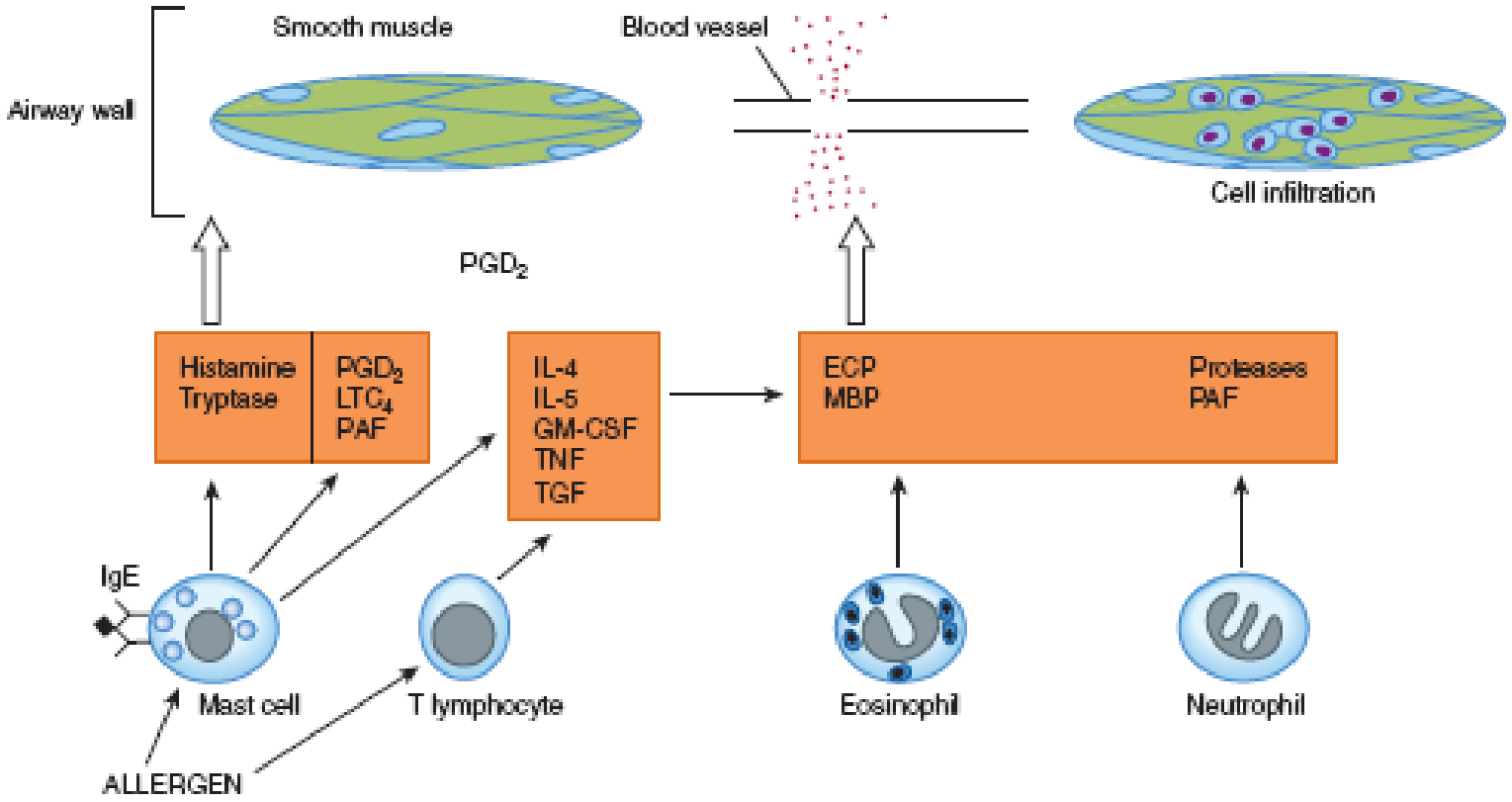
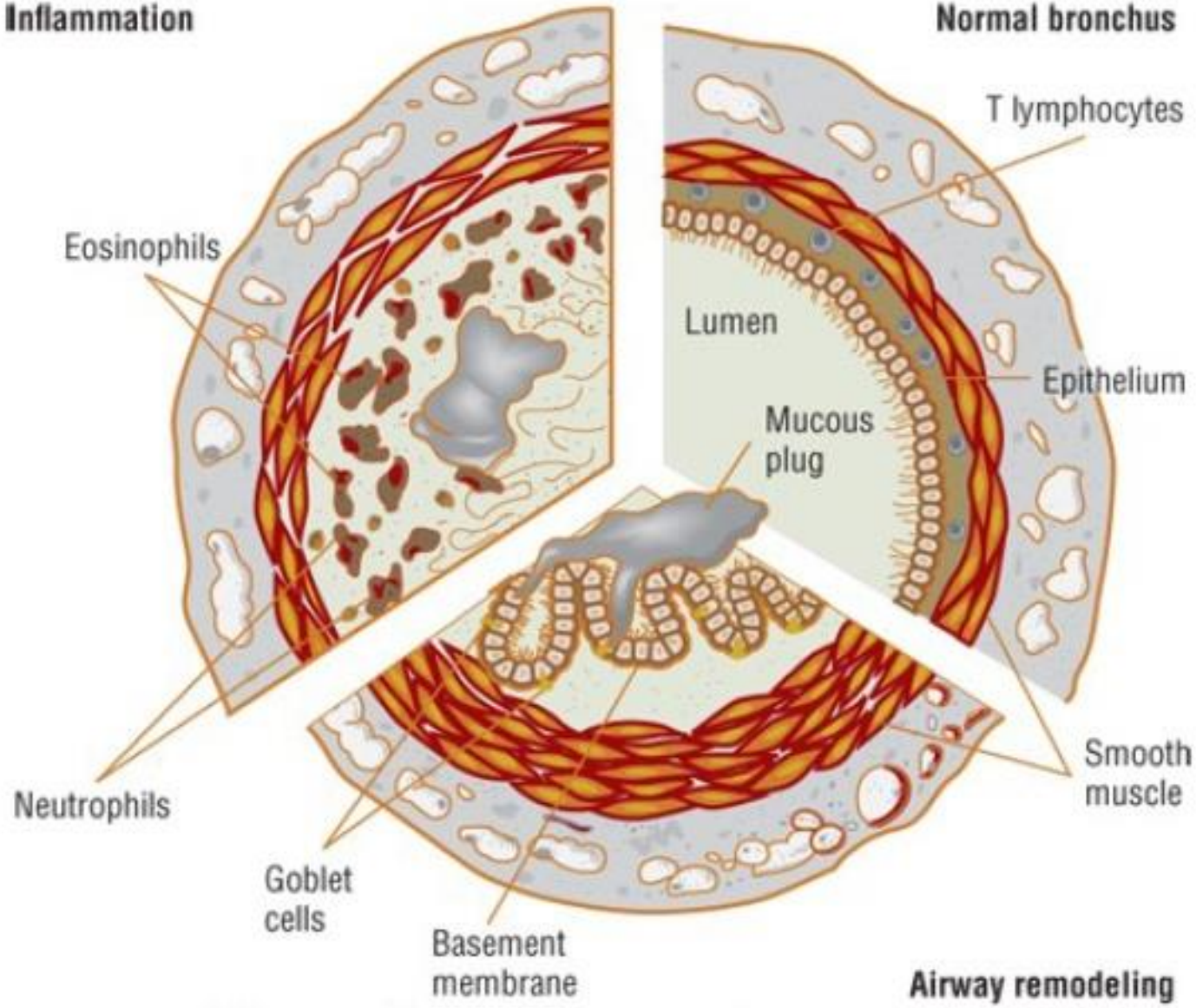

Airway wall
Smooth muscle
Blood vessel
Cell infiltration
PGD_2
Histamine
Tryptase
PGD_2
LTC_4
PAF
IL-4
IL-5
GM-CSF
TNF
TGF
ECP
MBP
Proteases
PAF
IgE
Mast cell
T lymphocyte
Eosinophil
Neutrophil
ALLERGEN

Figure :

Conceptual model for the immunopathogenesis of asthma. Exposure to allergen causes synthesis of IgE, which binds to mast cells in the airway mucosa. On reexposure to allergen, antigen-antibody interaction on mast cell surfaces triggers release of mediators of anaphylaxis: histamine, tryptase, prostaglandin D_2 (PGD_2), leukotriene C_4, and platelet-activating factor (PAF). These agents provoke contraction of airway smooth muscle, causing the immediate fall in FEV_1 . Reexposure to allergen also causes the synthesis and release of a variety of cytokines: interleukins 4 and 5, granulocyte-macrophage colony-stimulating factor (GM-CSF), tumor necrosis factor (TNF), and tissue growth factor (TGF) from T cells and mast cells. These cytokines in turn attract and activate eosinophils and neutrophils, whose products include eosinophil cationic protein (ECP), major basic protein (MBP), proteases, and platelet-activating factor. These mediators cause the edema, mucus hypersecretion, smooth muscle contraction, and increase in bronchial reactivity associated with the late asthmatic response, indicated by a second fall in FEV_1 3-6 hours after the exposure.


Inflammation
Normal bronchus
T lymphocytes
Eosinophils
Lumen
Epithelium
Mucous plug
Smooth muscle
Neutrophils
Goblet cells
Basement membrane
Airway remodeling

Pathophysiology of Bronchial Asthma

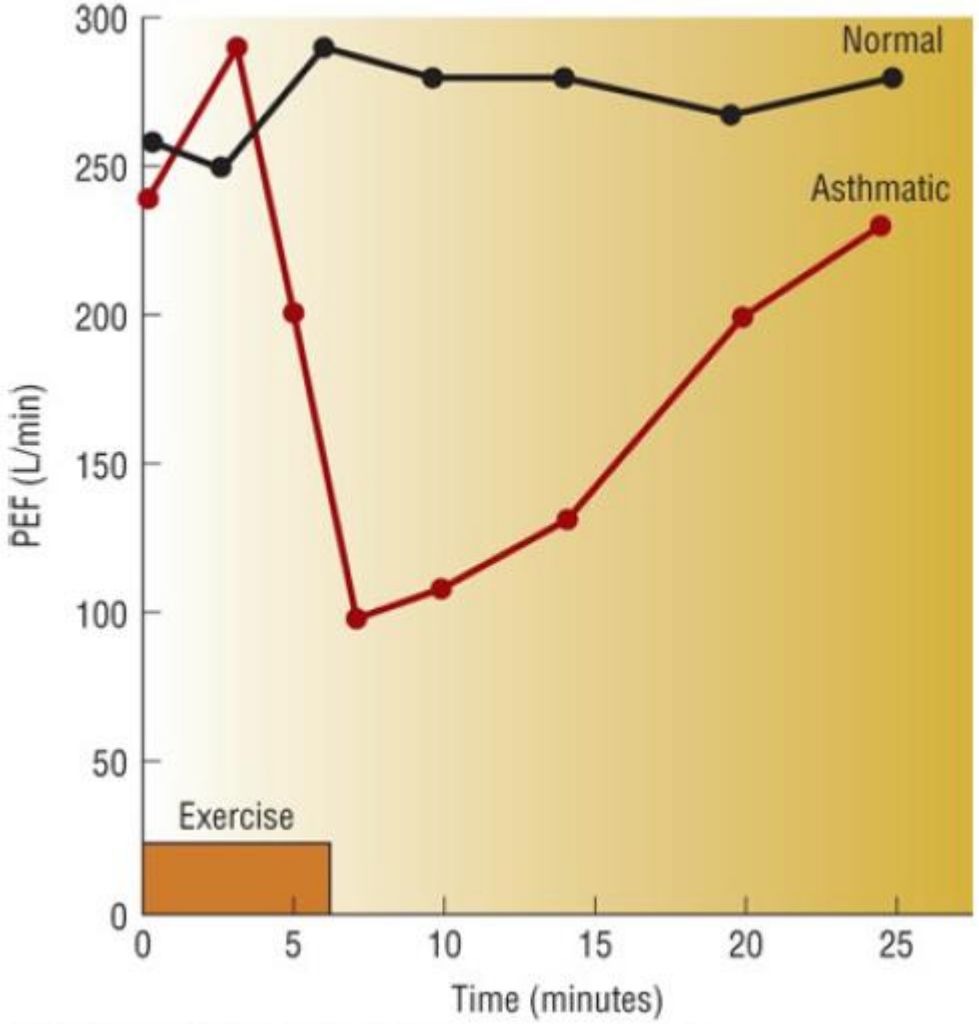
Remodeling of the Airways:

- **Remodeling presents as extracellular matrix fibrosis, an increase in smooth muscle and mucous gland mass, and angiogenesis.**
- **Tryptase (a smooth muscle mitogen) plays a role in airway remodeling.**
- **Airway remodeling represents an irreversible process.**

Pathophysiology of Bronchial Asthma

Exercise-Induced Bronchospasm (EIB):

- **EIB is defined as a drop in FEV1 of 10% or greater from pre-exercise value.**
- **The exact pathogenesis of EIB is unknown.**
- **Studies have demonstrated increased plasma histamine, cysteinyl leukotrienes, prostaglandins, and tryptase concentrations during EIB, suggesting a role for mast cell degranulation.**
- **EIB is provoked more easily in cold, dry air, and airborne particulate matter.**
- **Warm, humid air can blunt or block it.**



Typical responses to exercise in a normal subject and an asthmatic subject. Note the initial bronchodilation. (PEF, peak expiratory flow)

Pathophysiology of Bronchial Asthma

Nocturnal Asthma:

- It represents worsening of asthma during sleep.
- It may be associated with diurnal patterns of endogenous cortisol secretion and circulating epinephrine.
- Factors that may worsen nocturnal asthma include allergies, gastroesophageal reflux, obstructive sleep apnea, and sinusitis, which must be considered when evaluating these patients.
- Experts consider nocturnal symptoms to be a sign of inadequately treated persistent asthma.

Factors Contributing To Asthma Severity

Respiratory infection:

- **Respiratory syncytial virus (RSV), rhinovirus, influenza, parainfluenza, *Mycoplasma pneumoniae, Chlamydia*.**

Allergens:

- **Airborne pollens (grass, trees, weeds), house dust mites, animal dander, rodents, cockroaches, fungal spores.**

Exercise:

- **Particularly in cold, dry climate.**

Factors Contributing To Asthma Severity

Environment:

- **Cold air, fog, ozone, sulfur dioxide, nitrogen dioxide, tobacco smoke (including 2nd and 3rd hand), wood smoke, energy efficient buildings (increase indoor air pollution), meteorological conditions related to climate change, scented home products, cleaners, and perfumes.**

Emotions:

- **Anxiety, stress, laughter.**

Factors Contributing To Asthma Severity

Occupational stimuli:

- **Bakers (flour dust); farmers (hay mold); spice and enzyme workers; occupational cleaners, printers, (arabic gum); chemical workers (azo dyes, anthraquinone, ethylenediamine, toluene diisocyanates, polyvinyl chloride); plastics, rubber, and wood workers (formaldehyde, western cedar, dimethylethanolamine, anhydrides).**

Factors Contributing To Asthma Severity

Drugs:

- Acetaminophen (paracetamol).
- Aspirin, NSAIDs (cyclooxygenase inhibitors).
- Sulfites, benzalkonium chloride.
- Nonselective β-blockers.
- WHY? Look it up!

Therapy of Bronchial Asthma

Aerosol Therapy for Asthma:

- **Aerosol delivery is a site-specific topical route.**

1. **Inhalation of short-acting β_2-agonists provides more rapid bronchodilation compared to par-enteral or oral administration. It also provides better protection against EIB.**
2. **Inhalational corticosteroids (ICSs) have also enhanced local lung actions and reduced systemic effects of corticosteroids.**

Therapy of Bronchial Asthma

- **Some agents (formoterol, salmeterol, and ipratropium bromide) are only effective by inhalation.**
- **Therefore, understanding of aerosol drug delivery is essential to optimal asthma therapy.**
- **You should be aware of this and teach patients how to use inhalers.**

Therapy of Bronchial Asthma

Acute Severe Asthma in the Emergency Department:

1. **It is important that therapy NOT be delayed.**
2. **Lung function testing (PEF or FEV1) should be monitored before treatment, and at 1-hour after start of treatment and then periodically until response is achieved or no further improvement is evident.**
3. **Oxygen saturation should be monitored closely, and oxygen therapy implemented when needed.**

Therapy of Bronchial Asthma

4. **Arterial blood gases are reserved for patients who are poorly responsive to initial treatment or deteriorating.**
5. **The primary therapy of acute exacerbations is pharmacologic, which includes (all):**

a. **short-acting inhaled β_2-agonists**
b. **systemic corticosteroids**
c. **inhaled ipratropium (when response is inadequate)**
d. **and O_2.**

- **Treatments are typically administered concurrently to facilitate rapid improvement.**

Therapy of Bronchial Asthma

Also pay attention to the following:

1. **Correction of dehydration.**
2. **Do NOT use sedatives because anxiety may be a sign of hypoxemia, which could be worsened by central nervous system depressants.**
3. **Antibiotics are NOT indicated because viral respiratory tract infections are the primary cause of asthma exacerbations.**

- **Antibiotics should be reserved for patients who have pneumonia.**

4. **Mycoplasma and Chlamydia are infrequent causes of severe asthma exacerbations but should be considered in patients with high O_2 requirements.**

Therapy of Bronchial Asthma

Short-Acting β_2-Agonists:

- The short-acting inhaled β_2-agonists are the most effective bronchodilators and the treatment of first choice for the management of acute severe asthma.
- In more severely obstructed patients, they can be used by nebulization.
- Continuous nebulization decreases the hospital admission rate, provides greater improvement in the FEV1 and PEF, and reduces duration of hospitalization when compared with intermittent (hourly) nebulized albuterol (salbutamol) in the same total dose.

Therapy of Bronchial Asthma

- **Intravenous β_2-agonists have NO role in the management of patients with severe exacerbations.**
- **Aerosolized β_2-agonists can also be delivered successfully through mechanical ventilator circuits to infants, children, and adults in respiratory failure secondary to severe airway obstruction.**

Therapy of Bronchial Asthma

- The β_2-agonists relax airway smooth muscle regardless of the mechanism of constriction.
- Regular treatment (four times daily) does NOT improve symptom control over as-needed use (prn) and is NOT indicated.
- Long-term administration of β_2-agonists does NOT reduce bronchial hyperresponsiveness (BHR).

Therapy of Bronchial Asthma

- **Short-acting inhaled selective β_2-agonists are also the first treatment of choice for EIB.**
- **They inhibit EIB in a dose-dependent fashion and provide complete protection for ~ 2-hour period following inhalation.**
- **Two inhalations prior to exercise prevent EIB completely.**

Therapy of Bronchial Asthma

Adverse Reactions:

1. **Initially, inhaled β_2-agonists produce vasodilation, worsening ventilation–perfusion mismatch, slightly lowering O_2 saturation or PaO_2.**
2. **β_2-Adrenergic stimulation, especially at high doses, activates Na^+-K^+- ATPase, gluconeogenesis, and insulin secretion, → a mild-to-moderate decrease in serum potassium, magnesium, and phosphate concentration (drives potassium into the cell).**

Therapy of Bronchial Asthma

3. **Tachycardia mediated in part by baroreceptor reflex mechanisms (as a result of the drop in blood pressure from vasodilation), as well as by direct stimulation of cardiac β_2-adrenoceptors and some β_1 stimulation at high concentrations.**

- **An elevated heart rate is NOT an indication to use lower doses or to avoid using inhaled β_2-agonists.**

Therapy of Bronchial Asthma

4. **Chronic administration leads to down regulation of β_2-receptors and a decreased binding affinity (desensitization) → tolerance.**

- **Tolerance reduces duration of action.**
- **It occurs within a week of regular administration and does NOT worsen with continued use.**
- **Systemic corticosteroid therapy can both prevent and partially reverse this effect.**
- **The use of ICSs have minimal ability to prevent tolerance to β_2-agonists.**

Therapy of Bronchial Asthma

Long-Acting Inhaled β_2-Agonists (LABAs):

- **Formoterol and salmeterol, provide long-lasting bronchodilation (≥ 12 hours).**
- **ULTRA-LABA (indacaterol, vilanterol, and olodaterol), have a 24-hour duration of effect.**
- **Increased respiratory deaths in salmeterol users have been reported.**

Therapy of Bronchial Asthma

Corticosteroids:

- **Systemic corticosteroids are indicated in all patients with acute severe asthma exacerbations, and should be administered within one hour of presentation.**
- **Clinical improvement is noted after ~ 4 hours.**
- **IV therapy offers NO therapeutic advantage over oral administration, except in patients who are too-dyspneic to swallow, who are vomiting, or who are intubated.**

Therapy of Bronchial Asthma

- **Adults are treated for 5 - 7 day, but children typically require only 3 - 5 days.**
- **Dexamethasone (1-2) doses *vs* a 5-day course of prednisolone may be an option for children and has the benefit of improving vomiting.**
- **Tapering the systemic corticosteroid dose following discharge from the hospital is unnecessary, in patients prescribed inhalational corticosteroids (ICSs) for outpatient therapy.**

Therapy of Bronchial Asthma

Systemic Corticosteroids:

Corticosteroids are the most effective anti-inflammatory agents to treat asthma.

Actions relevant to bronchial asthma include:

1. **Increased number and responsiveness of β_2-adrenergic receptors .**
2. **Reduced mucus production and hypersecretion.**
3. **Reduced bronchial hyper-responsiveness (BHR).**
4. **Reduced airway edema and exudation.**

Therapy of Bronchial Asthma

5. **Glucocorticoids repress pro-inflammatory genes encoding cytokines, chemokines, cell adhesion molecules, inflammatory enzymes and receptors.**
6. **Decreased vascular permeability.**

Therapy of Bronchial Asthma

- **The time required to see a particular effect is variable, depending on the time required for: new protein synthesis, decreased formation of the particular mediator, and resolution of the inflammatory response.**
- **Cellular and biochemical effects are immediate, but the time required to produce a clinical response is variable.**
- **β_2-Receptor density increases within 4 hours of corticosteroid administration, while improved responsiveness to β_2-agonists occurs within 2 hours.**

Therapy of Bronchial Asthma

- **In acute severe asthma, 4-12 hours are required before clinical response is noted.**
- **Reversal of increased BHR requires at least 1 week of therapy.**
- **Drugs used include prednisone, methylprednisolone and dexamethasone.**

Some Adverse effects of systemic corticosteroids

1. Suppression of the hypothalamic-pituitary-adrenal axis.
2. Growth retardation.
3. Skeletal muscle myopathy.
4. Osteoporosis and fractures.
5. Aseptic bone necrosis.
6. Pancreatitis.
7. Pseudotumor cerebri.
8. Psychiatric disturbances.
9. Sodium and water retention.
10. Hypokalemia
11. Hyperglycemia
12. Hypertension
13. Impaired wound healing
14. Immunosuppression
15. Glaucoma
16. Posterior subcapsular cataract
17. Central redistribution of fat
18. Moon face
19. etc

Therapy of Bronchial Asthma

Inhaled Corticosteroids:

- **The ICSs have high anti-inflammatory potency, approximately 1,000-fold greater than endogenous cortisol.**
- **Aerosol delivery of the preparations is remarkably variable, ranging from 10-60%.**
- **Different devices for the same chemical entity may result in two-fold differences in delivery, so you should be careful when changing devices.**

Therapy of Bronchial Asthma

- **The ICSs that are currently available for use are: beclomethasone dipropionate, budesonide, ciclesonide, flunisolide, fluticasone propionate, fluticasone furoate, and mometasone furoate.**
- **Because they are lipophylic, systemic clearance of the available ICSs is very rapid (~ the rate of liver blood flow).**
- **Ciclesonide is inactivated also by blood esterases.**

Therapy of Bronchial Asthma

- **Some of the drug will be deposited in oral mucosa and get absorbed through GIT.**
- **Therefore, mouth rinsing and spitting will reduce their oral bioavailability.**

Therapy of Bronchial Asthma

- **The ICSs are considered the preferred long-term control therapy for persistent asthma in all patients.**
- **Low- to medium-dose ICSs reduce BHR, improve lung function, and reduce severe exacerbations leading to reduced ED visits and hospitalizations.**
- **They do NOT reduce airway remodeling and loss of lung function seen in patients with persistent asthma.**

Therapy of Bronchial Asthma

- **For patients inadequately controlled on low-dose ICSs, the dose may be increased.**
- **Alternatives: addition of leukotriene receptor antagonists (LTRAs) or theophylline to ICSs.**
- **Doses of ICSs in the high range significantly enhance the risk of toxicity.**
- **High doses of ICSs plus LABA are reserved for patients with severe persistent asthma.**

Therapy of Bronchial Asthma

Beneficial effects of inhaled corticosteroids:

1. **Decreased eosinophil and mast cell number.**
2. **Decrease T-lymphocyte cytokine production.**
3. **Inhibit transcription of inflammatory genes.**
4. **Reduce endothelial cell leak.**
5. **May up-regulate β_2-receptors.**
6. **Reduce airway epithelial sub-basement membrane thickening.**

Therapy of Bronchial Asthma

The response to ICSs is delayed:

- **Most symptoms will improve in the first 1-2 weeks of therapy and maximum improvement will be reached in 4-8 weeks.**
- **Improvement in baseline FEV1 and PEF may require 3 to 6 weeks for maximum improvement.**
- **Improvement in BHR requires 2-3 weeks and approaches maximum in 1-3 months but may continue to improve over 1 year.**
- **Sensitivity to exercise challenge decreases after 4 weeks of therapy.**

Some Potential Adverse Effects of inhaled corticosteroids

1. Hoarseness, dysphonia (myopathy of vocal cords)
2. Oral thrush (candida fungal infection).
3. Growth retardation
4. Myopathy.
5. Osteoporosis, fractures and aseptic necrosis of the hip.
6. Posterior sub-capsular cataract and glaucoma.
7. Adrenal axis suppression.
8. Immuno-suppression and impaired wound healing.
9. Easy bruising and skin striae.
10. Hyperglycemia and hypokalemia.
11. Hypertension.
12. Psychiatric disturbances.

Anticholinergics

- **Unlike β_2-agonists, they are NOT functional antagonists; they only reverse cholinergic-mediated bronchoconstriction (bronchial tone is maintained by parasympathetic nerves).**
- **A number of the triggers and mediators of asthma produce bronchoconstriction in part through vagal reflex mechanisms (histamine, prostaglandins, sulfur dioxide, exercise, and allergens).**

Anticholinergics

- **Anticholinergics have NO effect on BHR.**
- **Anticholinergics attenuate but do NOT block EIB.**
- **Ipratropium bromide is a nonselective antagonist of muscarinic receptors → bronchodilation (M_3-receptors).**
- **Blockade of presynaptic M_2-receptors allows the release of acetylcholine → paradoxical bronchoconstriction.**

Anticholinergics

- **The quaternary ammonium derivatives (ipratropium bromide and tiotropium) have little absorption across respiratory mucosa and do NOT penetrate the blood–brain barrier, thus they have negligible systemic effects with a prolonged local effect.**
- **They also do NOT significantly affect mucociliary clearance or respiratory secretions.**

Anticholinergics

- **Duration of action of Ipratropium bromide is 4-8 hours, while that of Tiotropium bromide is 24 hours.**
- **Ipratropium bromide is only indicated as adjunctive therapy in acute severe asthma NOT completely responsive to β_2-agonists alone, which may produce further improvement in lung function.**
- **It is also important in COPD to reverse vagus-mediated bronchoconstriction.**

Anticholinergics

- **When used via nebulizer, and if a tight mask or mouthpiece is NOT used, ipratropium bromide that deposits in the eyes may produce dilation of pupil and difficulty in accommodation.**

Theophylline

- **It has been used for asthma therapy for more than 50 years.**
- **Its use has much declined because of the high risk of severe life-threatening toxicity and numerous drug interactions.**
- **Theophylline is a moderately potent bronchodilator with mild anti-inflammatory properties.**

Theophylline

- **Like β_2-agonists, theophylline is a functional bronchodilator.**
- **Preferably used as sustained-release product orally, or by short IV infusion as aminophylline (theophylline ethylenediamine).**
- **It stimulates endogenous catecholamine release.**
- **Theophylline therapeutic concentration is 5 -15 µg/mL.**
- **It has a low therapeutic index.**

Theophylline

- **Sustained-release theophylline is less effective than ICSs and NOT more effective than oral sustained-release β_2-agonists or Leukotriene antagonists.**
- **The addition of theophylline to ICSs is similar to doubling the dose of the ICS, and is less effective than LABAs as adjunctive therapy.**
- **The addition of theophylline to patients with poorly controlled asthma receiving ICS/LABA combination does NOT improve outcomes.**

Theophylline

- **Toxicities include caffeine-like effects of nausea, vomiting, tachycardia, jitteriness, and difficulty sleeping to more severe toxicities such as cardiac tachyarrhythmias and seizures.**
- **Theophylline is eliminated primarily by metabolism via cytochrome P450s (mainly CYP1A2 and CYP3A3).**

Theophylline

Theophylline clearance varies widely:

1. **In normal adults, the mean plasma clearance is 0.69 mL/kg/min.**
2. **Children clear theophylline faster than adults (1–1.5 mL/kg/min).**
3. **Neonates and young infants have the slowest clearance.**
4. **Even within the same age groups, theophylline clearance can vary 2-3 folds.**
5. **Even when maintenance doses are modified to correct for the above factors, plasma concentrations vary widely.**

Theophylline

Drug Interactions:

Drugs that reduce theophylline clearance:

- **Cimetidine, eryhtromycin, clarithromycin, allopurinol, propranolol, interferon, thiabendazole, ticlopidine, zileuton, quinolones.**

Drugs that increase theophylline clearance:

- **Rifampin, phenobarbital, carbamazepine, phenytoin, charcoal-broiled meat, high-protein diet, smoking, sulfinpyrazone, moricizine.**

Leukotriene Modifiers

- **Two cysteinyl-LT receptor antagonists (zafirlukast and montelukast) and one 5-lipoxygenase inhibitor (zileuton) are available.**
- **They reduce allergen-, exercise-, cold air-, hyperventilation-, irritant-, and aspirin-induced asthma.**
- **Zileuton use is limited due to hepatic toxicity and inhibition of CYP3A4 isoenzymes (drug interactions).**

Leukotriene Modifiers

- **These drugs improve pulmonary function tests (FEV1 and PEF), decrease nocturnal awakenings, decrease β_2-agonist use, and improve asthma symptoms.**
- **They are effective orally, and can be used once or twice a day.**
- **They may be specially useful in patients with aspirin-sensitive asthma.**

Leukotriene Modifiers

- **Montelukast may be used for EIB in adults, but it is less effective than short-acting inhaled β_2-agonists.**
- **NOT that effective in adults with severe uncontrolled asthma.**
- **They are NOT as effective as LABAs when added to ICSs for moderate persistent asthma.**
- **They are less effective in asthma than low doses of ICSs.**

Leukotriene Modifiers

Adverse effects:

- **A rare idiosyncratic syndrome similar to the Churg-Strauss syndrome (eosinophilia, heart failure, and eosinophilic vasculitis) has been reported with zafirlukast and montelukast.**
- **Neuropsychiatric events (suicidal thoughts).**
- **Fatal hepatic failure (zafirlukast).**

Anti-IgE (Omalizumab)

- **It is a recombinant anti-IgE monoclonal antibody that can be used for the treatment of allergic asthma NOT well controlled with oral corticosteroids or ICSs.**
- **It prevents the binding of IgE to its high-affinity receptor on mast cells and basophils.**
- **This action leads to a decrease in the release of mediators in response to allergen exposure.**

Anti-IgE (Omalizumab)

- **It decreases IgE receptor expression on basophils and airway submucosal mast cells over 8 to 12 weeks.**
- **It is administered subcutaneously (peak serum concentration is achieved in 3-14 days).**
- **It is eliminated primarily through the reticuloendothelial system and has an elimination half-life of ~ 20 days.**
- **It should be administered under strict medical observation with drugs for treating anaphylaxis available.**

Anti-IgE (Omalizumab)

- **It can be used in patients with allergic asthma > than 6 years of age.**
- **It is very expensive.**
- **Therapy is associated with a 0.2% rate of anaphylaxis.**
- **Anaphylaxis may occur up to 24 hours following injection.**

Therapy of Anemias

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Introduction

- **Anemia is a group of diseases characterized by a decrease in either hemoglobin (Hb) or the volume of red blood cells (RBCs), which results in decreased oxygen-carrying capacity of the blood.**
- **Anemia is defined by the World Health Organization (WHO) as Hb less than 13 g/dL in men and less than 12 g/dL in women.**
- **According to the WHO, 25% of the world's population are anemic.**

Introduction

- **Acute-onset anemia presents with tachycardia, lightheadedness, and dyspnea, while chronic anemia presents with weakness, fatigue, headache, vertigo, and pallor.**
- **Iron deficiency is the leading cause of anemia worldwide, accounting for about 50% of cases.**
- **It is recommended to routinely screen for iron deficiency anemia, especially in pregnant women, children, and the elderly.**

Introduction

- **Anemia can result from inadequate RBC production, increased RBC destruction, or blood loss.**
- **It can be a manifestation of other systemic disorders, such as infection, chronic renal dysfunction, or malignancy.**
- **Because anemia is a sign of underlying pathology, early identification of the cause is essential.**

Iron Deficiency Anemia

- **The reference ranges for Hb and Hct are wide, so that a patient may lose up to 15% of RBC mass and the Hct is still within the reference range.**
- **Therefore, iron deficiency may precede the appearance of anemia.**

Iron Balance:

- **The normal iron content of the body is about 3 - 4 g.**
- **Iron is a component of Hb, myoglobin, and cytochromes.**

Iron Content in the Body

	Iron (mg)
Hb	2000
Myoglobin	130
Transferrin (plasma)	3
Ferritin (storage)	1000
Cytochromes	Rest of iron

Iron Deficiency Anemia

- Iron loss is ~ 1 mg daily.
- Menstruating women lose more per day.
- Pregnancy requires an additional 700 mg of iron.
- Blood donation results in ~ 250 mg of iron loss.
- Iron is best absorbed in its ferrous (Fe^{2+}) form.
- The normal daily diet contains mainly the ferric (Fe^{3+}) non-absorbable form.

Iron Deficiency Anemia

- **Iron is ionized by gastric acid, and then reduced to the Fe^{2+} state before it is absorbed.**
- **It is absorbed primarily in the duodenum.**
- **The recommended daily intake of elemental iron is 8 mg in adult males and postmenopausal females, and 18 mg in menstruating females.**
- **Children require more iron because of growth related increases in blood volume.**

Iron Deficiency Anemia

- **Pregnant women require more iron because of fetal development.**
- **Normally, only the amount of iron lost per day is absorbed.**
- **Hem iron (in meat, fish, and poultry) is about three times more absorbable than the non-hem iron found in vegetables, fruits, dried beans, nuts, grains, and dietary supplements.**
- **Gastric acid and ascorbic acid increase the absorption of non-hem iron.**

Iron Deficiency Anemia

- Dietary components that form insoluble complexes with iron (phytates, tannates, and phosphates) decrease absorption.
- Polyphenols bind iron and decrease non-hem iron absorption when large amounts of tea or coffee are consumed with a meal.
- Calcium inhibits absorption of both hem and non-hem iron (mechanism ?).
- Patients with gastrectomy or achlorhydria have decreased iron absorption.

Iron Deficiency Anemia

- **Iron deficiency results from increased iron demand (hematopoiesis), increased loss, decreased intake or decreased absorption.**
- **Iron stores are reduced before reduced serum iron levels, and can be assessed with serum ferritin measurement.**
- **Groups at risk: children younger than 2 years, adolescent girls, pregnant and lactating females, and those older than 65 years.**

Iron Deficiency Anemia

- **In patients older than 65 years of age test for occult GI bleeding.**
- **Medications involved: alcohol, corticosteroids, anticoagulants, aspirin, and other (NSAIDs).**
- **Other causes of hypochromic microcytic anemia include: "anemia of inflammation", thalassemia, sideroblastic anemia, and heavy metal (lead) poisoning.**

Therapy of Iron Deficiency Anemia

Treatment:

- **Desired outcomes: reversal of hematologic parameters to normal, return of normal function and quality of life, and prevention or reversal of long-term complications.**
- **Treatment is focused on replenishing iron stores.**
- **Treatment of the underlying cause is needed as it aids in the correction of iron deficiency.**

Therapy of Iron Deficiency Anemia

- **Treatment consists of use of soluble and absorbable Fe^{2+} iron salts.**
- **Meat, fish, and poultry, and certain iron-fortified cereals can help treat IDA.**
- **Tolerance of iron salts may improve with a small initial dose and gradual escalation to the full dose.**
- **The recommended dose is about 150 to 200 mg of elemental iron daily, in two or three divided doses.**

Therapy of Iron Deficiency Anemia

- **Iron preferably is administered at 1 hour before meals because food can interfere with absorption. (???)**
- **Many patients take iron with food because of GI upset when iron is administered on an empty stomach.**
- **Treatment should continue for 3 to 6 months after the anemia is resolved to allow for repletion of iron stores and to prevent relapse.**

Iron Salt	Percent Elemental Iron	Common: Formulations and Elemental Iron Provided
Ferrous sulfate	20	60-65 mg/324-325 mg tablet 60 mg/5 mL syrup 44 mg/ 5 mL elixir 15 mg/1 mL
Ferrous sulfate (disiccated)	30	65 mg/200 mg tablet 50 mg/160 mg tablet
Ferrous gluconate	12	38 mg/325 mg tablet 28-29 mg/240-246 mg tablet
Ferrous fumarate	33	66 mg/200 mg tablet 106 mg/324-325 mg tablet

Therapy of Iron Deficiency Anemia

Adverse reactions:

- **At therapeutic doses:**

1. **dark discoloration of stool**
2. **constipation or diarrhea**
3. **nausea and vomiting**

- **GI adverse effects are dose-related and are similar among iron salts when equivalent amounts of elemental iron are administered.**

Drug Interactions with Iron Salts

Drugs That Decrease Iron Absorption	Drugs Affected by Iron
1. Al^{+3} -, Mg^{+2} - , and Ca^{2+} - containing antacids. 2. Tetracycline and doxycycline. 3. Histamine H_2 -receptor antagonists. 4. Proton-pump inhibitors. 5. Cholestyramine.	1. Levodopa ↓ (chelates with iron). 2. Methyldopa absorption is decreased. 3. Levothyroxine absorption is decreased. 4. Penicillamine ↓ (chelates with iron). 5. Fluoroquinolones ↓ (forms ferric ion quinolone complex). 6. Tetracycline and doxycycline ↓ (when administered within 2 hours of iron salt). 7. Mycophenolate ↓ (decreases absorption).

Therapy of Iron Deficiency Anemia

Common causes of treatment failure:

1. **Poor patient adherence.**
2. **Inability to absorb iron (due to previous gastrectomy, gastric bypass surgery, or celiac disease).**
3. **Persistance of a coexisting cause of anemia (continued bleeding. …).**
4. **Incorrect diagnosis.**

Therapy of Iron Deficiency Anemia

Parenteral Iron Therapy:

Indications:

1. Intolerance to oral iron.
2. Malabsorption of iron.
3. Nonadherence to oral iron.
4. Patients with chronic kidney disease especially those undergoing hemodialysis.

Therapy of Iron Deficiency Anemia

5. **Patients with inflammatory bowel disease and those with gastric bypass/gastric resection due to poor oral absorption (first-line).**
6. **Cancer patients receiving chemotherapy and erythropoiesis-stimulating agents.**

Therapy of Iron Deficiency Anemia

Parenteral iron preparations:

1. **Iron dextran.**
2. **Sodium ferric gluconate.**
3. **Iron sucrose.**
4. **Ferumoxytol.**
5. **Ferric carboxymaltose.**

- **They are all effective, but may differ in adverse effect profiles.**

Therapy of Iron Deficiency Anemia

- **All parenteral iron preparations carry a risk for severe anaphylactic reactions, which is more with iron dextran and ferumoxytol products.**
- **Resuscitation equipment and trained staff should be available during administration of all iron dextran preparations.**

Parenteral iron dosing

Hemoglobin iron deficit (mg) = BW x (14 - Hgb) x (2.145) + iron to replenish stores if desired (mg)

- **An additional quantity of iron to replenish stores is about 600 mg for women and 1,000 mg for men.**
- **The concentration of elemental iron in the various products [iron dextran: 50 mg/mL; iron sucrose: 20 mg/mL; ferric gluconate: 12.5 mg/mL; ferumoxytol: 30 mg/mL; ferric carboxymaltose: 50 mg/mL].**
- **Reference: uptodate.com**

Megaloblastic Anemias

- **Macrocytosis seen in megaloblastic anemias is caused by abnormal DNA metabolism resulting from vitamin B_{12} or folate deficiency.**
- **With adequate folate and vitamin B_{12} levels and the absence of liver disease, high alcohol intake may produce macrocytosis.**
- **Cessation of alcohol results in resolution of the macrocytosis within ~ 2 months.**

Megaloblastic Anemias

- **Drug-induced macrocytosis:**

  hydroxyurea, zidovudine, cytarabine, methotrexate, azathioprine, 6-mercaptopurine, cladribine.

- **In vitamin B_{12}- or folate-deficiency anemia, megaloblastosis results from interference with folic acid- and vitamin B_{12}-interdependent nucleic acid synthesis in the immature erythrocyte.**

Megaloblastic Anemias

- **The maturation process is impaired, resulting in immature large RBCs (macrocytosis).**
- **RNA and DNA synthesis depend on a series of reactions catalyzed by vitamin B_{12} and folic acid because of their role in the conversion of uridine to thymidine.**

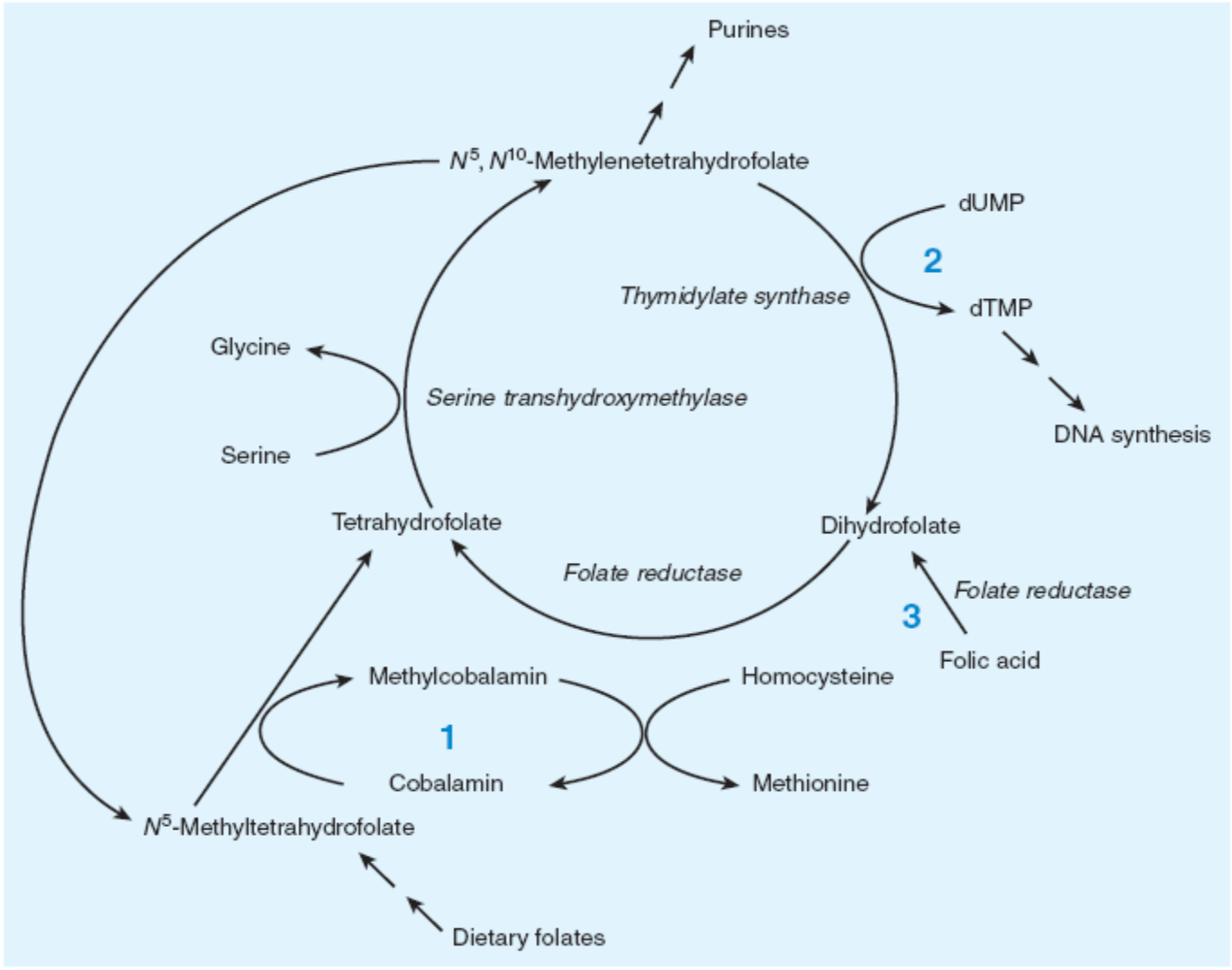

FIGURE 33–3 Enzymatic reactions that use folates. **Section 1** shows the vitamin B_{12}-dependent reaction that allows most dietary folates to enter the tetrahydrofolate cofactor pool and becomes the "folate trap" in vitamin B_{12} deficiency. **Section 2** shows the dTMP cycle. **Section 3** shows the pathway by which folic acid enters the tetrahydrofolate cofactor pool. Double arrows indicate pathways with more than one intermediate step.

Vitamin B_{12} Deficiency Anemia

Causes:

1. **Inadequate intake.**

- **In strict vegans and their breast-fed infants, chronic alcoholics, and elderly patients who consume a "tea and toast" diet because of financial limitations or dental problems.**

Vitamin B_{12} Deficiency Anemia

2. **Decreased absorption.**

a) **With loss of intrinsic factor by autoimmune mechanisms (pernicious anemia, in which gastric parietal cells are selectively damaged).**

b) **With Inadequate gastric acid production, or use of antacid drugs (proton pump inhibitors and histamine H_2-receptor antagonists), leading to failure of cleavage and release of vitamin B_{12} from proteins in food.**

Vitamin B_{12} Deficiency Anemia

c) In chronic atrophic gastritis, or gastric surgery.

d) Helicobacter pylori infection (a cause of chronic gastritis).

e) Overgrowth of bacteria and parasites that use vitamin B_{12} in the bowel.

f) Metformin may reversibly decrease B_{12} absorption, due to its effects on the mechanism of absorption of vitamin B_{12}-receptor complex in the terminal ileum.

Vitamin B_{12} Deficiency Anemia

g) **Injury or surgical removal of ileal receptor sites where vitamin B_{12} and the intrinsic factor complex are absorbed (Crohn's disease or small bowel surgery).**

Vitamin B_{12} Deficiency Anemia

- Vitamin B_{12} is a water-soluble vitamin obtained by ingestion of meat, fish, poultry, dairy products, and fortified cereals.
- The body stores vitamin B_{12} is in the liver for several years (2000 – 4000 µg).
- The recommended daily requirement is 2 µg in adults and 2.6 µg in pregnant or breast-feeding women.
- Vitamin B_{12} deficiency usually takes several years to develop following vitamin deprivation.

Vitamin B_{12} Deficiency Anemia

Vitamin B_{12} deficiency also causes :

1. **Neurologic complications (bilateral paraesthesia in extremities, and deficits in proprioception and vibration). If not treated, symptoms progress to ataxia, dementia-like symptoms, psychosis, and vision loss.**
2. **In children prolonged deficiency can lead to poor brain development.**

- **Patients with unexplained neuropathies should be screened for vitamin B_{12} deficiency.**

Vitamin B_{12} Deficiency Anemia

Megaloblastic anemia is associated with:

1. **Elevated MCV.**
2. **Mild leukopenia and thrombocytopenia.**
3. **Low serum vitamin B_{12} level, less than 200 pg/mL.**
4. **Subclinical vitamin B_{12} deficiency is sometimes seen with vitamin B_{12} levels 200 - 300 pg/mL.**

Vitamin B_{12} Deficiency Anemia

- **Methylmalonic acid (MMA) and homocysteine are first to accumulate in vitamin B_{12} deficiency.**
- **Elevations in MMA are more specific for vitamin B_{12} deficiency.**

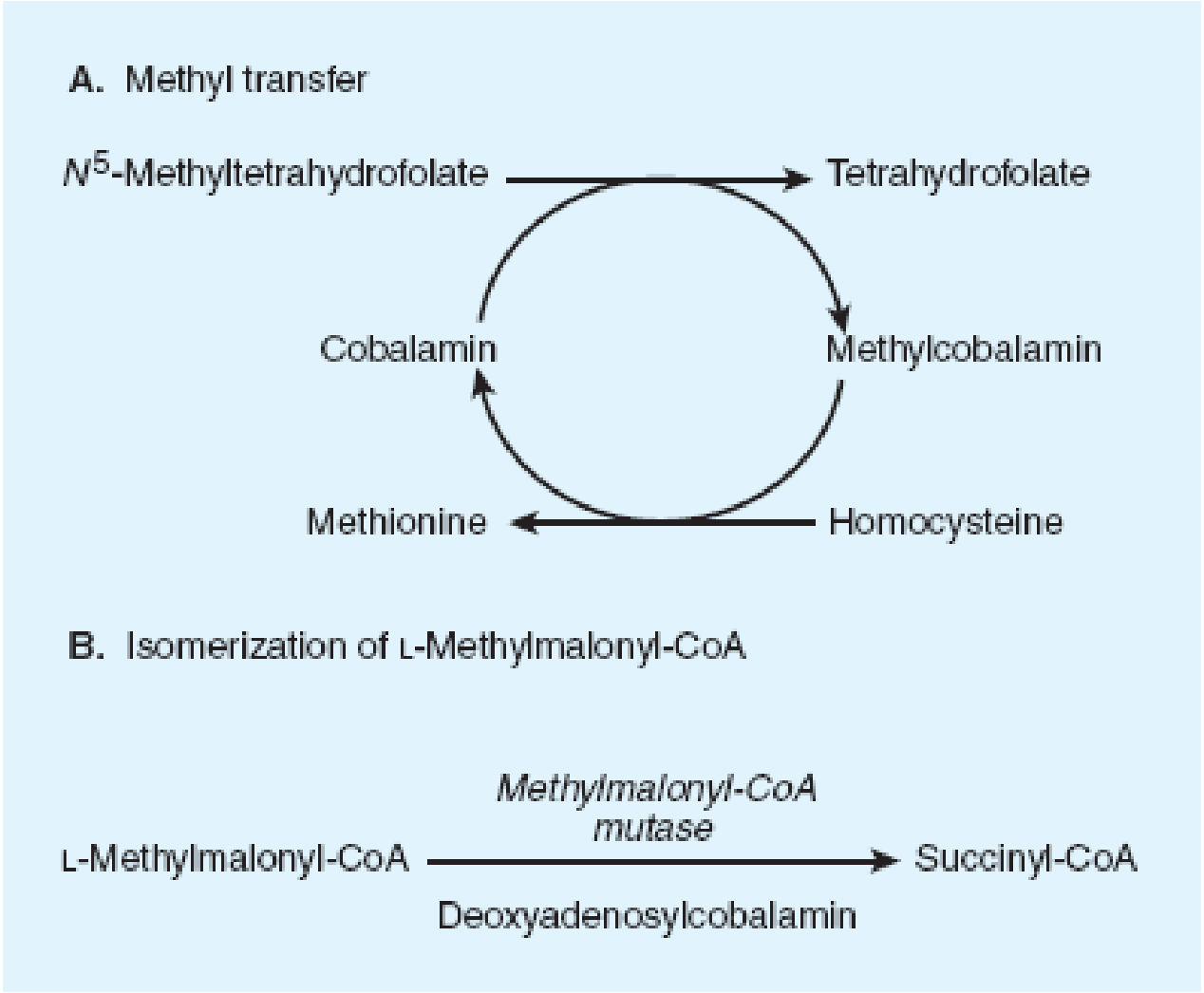

FIGURE 33–2 Enzymatic reactions that use vitamin B_{12}. See text for details.

Vitamin B_{12} Deficiency Anemia

- **Homocysteine can also be elevated in folate deficiency, chronic renal disease, alcoholism, smoking, and use of steroid or cyclosporine therapy.**
- **Hyperhomocysteinemia may be an independent risk factor for cerebrovascular, peripheral vascular, coronary, and venous thromboembolic diseases.**

Vitamin B_{12} Deficiency Anemia

Treatment:

- **The goals of treatment for vitamin B_{12} deficiency include:**

a. **reversal of hematologic manifestations.**

b. **replacement of body stores.**

c. **prevention or resolution of neurologic manifestations.**

- **Early treatment is very important because neurologic damage may be reversible if the deficiency is detected and corrected early.**

Vitamin B_{12} Deficiency Anemia

- **The underlying etiology should be corrected also.**
- **Parenteral vitamin B_{12} regimen consists of daily injections of 1,000 µg of cyanocobalamin for 1 week to saturate vitamin B_{12} stores in the body and resolve clinical manifestations of the deficiency.**
- **Thereafter, it can be given weekly for 1 month, and then monthly for maintenance.**

Vitamin B_{12} Deficiency Anemia

- **Parenteral therapy is indicated in the presence of neurologic symptoms.**
- **Vitamin B_{12} should be continued for life in patients with pernicious anemia (intrinsic factor deficiency).**

Adverse effects:

- **Are rare, and include hyperuricemia and hypokalemia due to marked increase in potassium utilization during production of new hematopoietic cells.**

Folic Acid Deficiency Anemia

Major causes of folic acid deficiency:

1. **Inadequate intake.**

- **Poor eating habits in elderly patients, teenagers ("junk food"), alcoholics, the poor, and those who are chronically ill, or demented.**

2. **Decreased absorption:**

- **In patients with malabsorption syndromes.**
- **Alcoholism.**

Folic Acid Deficiency Anemia

- **In alcoholics with poor dietary habits, alcohol:**

a) **interferes with folic acid absorption**

b) **interferes with folic acid utilization at the cellular level**

c) **decreases hepatic stores of folic acid.**

Folic Acid Deficiency Anemia

3. **Increased requirements:**

- **When the rate of cellular division is increased as seen in:**

a) **Pregnant women.**
b) **Patients with hemolytic anemia.**
c) **Adolescents and infants during their growth spurts.**
d) **Malignancy.**
e) **Others**

Folic Acid Deficiency Anemia

Drug-induced folic acid deficiency:

1. **Folate antagonists; methotrexate; pentamidine, trimethoprim, and triamterene.**
2. **Phenytoin, phenobarbital, and primidone may reduce absorption through the intestine.**

Folic Acid Deficiency Anemia

- **Major dietary sources of folate include fresh, green leafy vegetables, citrus fruits, yeast, mushrooms, dairy products, and animal organs such as liver and kidney.**
- **The minimum daily requirement is 50 to 100 µg.**
- **Because the body stores about 5 to 10 mg of folate, primarily in the liver, cessation of dietary folate intake can result in deficiency within 3 to 4 months.**

Folic Acid Deficiency Anemia

- **In the general population, the recommended daily allowance for folate is 600 µg for pregnant females, 400 µg in nonpregnant females, and 500 µg for lactating women.**

Folic Acid Deficiency Anemia

- **It is important to rule out vitamin B_{12} deficiency when folate deficiency is suspected.**
- **Laboratory changes associated with folate deficiency are similar to those seen in vitamin B_{12} deficiency, except vitamin B_{12} and MMA levels which may be normal.**
- **Serum folate levels decrease to less than 3 ng/mL within a few days of reduced dietary folate intake.**

Folic Acid Deficiency Anemia

- **If serum or erythrocyte folate levels are borderline, serum homocysteine usually is increased with a folic acid deficiency.**
- **If serum MMA levels also are elevated, vitamin B_{12} deficiency must be ruled out since folate does not participate in MMA metabolism.**

Folic Acid Deficiency Anemia

- **Therapy for folic acid deficiency consists of administration of exogenous folic acid to:**

1. **induce hematologic remission.**
2. **replace body stores.**
3. **resolve signs and symptoms.**

- **In most cases, 1 mg daily orally is sufficient to replace stores.**

Folic Acid Deficiency Anemia

- **In cases of deficiency due to malabsorption, doses of 1 to 5 mg daily may be necessary.**
- **Folic acid is completely absorbed by the GI tract and is converted to tetrahydrofolate.**
- **Therapy should continue for about 4 months.**

Folic Acid Deficiency Anemia

- **Foods high in folic acid should also be encouraged (Beef liver, cooked lentils, chickpeas, fortified cereals, cooked spinach, kidney beans, tomato juice, orange, ..).**
- **Long-term folate administration may be necessary in increased folate requirements.**
- **Low-dose folate therapy (500 mcg daily) can be given in combination with anticonvulsant drugs.**
- **Significant adverse effects have not been reported.**

Folic Acid Deficiency Anemia

- **Periconceptional folic acid supplementation is recommended to decrease the occurrence and recurrence of neural tube defects, specifically anencephaly and spinal bifida.**
- **Folic acid supplementation at a dose of 400 mcg daily is recommended for all women.**

Folic Acid Deficiency Anemia

- **Women who have previously given birth to offspring with neural tube defects or those with a family history of neural tube defects should ingest 4 mg daily of folic acid.**
- **Folic acid supplementation should NOT be attained via ingestion of excess multivitamins because of the risk of fat soluble vitamin toxicity.**

Anemia of Inflammation

- **It describes both “anemia of chronic disease” and “anemia of critical illness”, to reflect the inflammatory process that underlies both of these types of anemia.**
- **The onset of anemia of critical illness is quicker, over days, and typically occurs in a hospital setting.**
- **Anemia of chronic disease has a similar mechanism, but it develops over months to years from a chronic condition.**

Anemia of Inflammation

- **It is especially important in the differential diagnosis of iron deficiency.**
- **Various conditions associated with "anemia of chronic disease" may predispose patients to blood loss (malignancy, GI blood loss from treatments with aspirin, NSAIDs, or corticosteroids).**

Common Causes of Anemia of Inflammation

1. Chronic infections
   Tuberculosis
   Other chronic lung infections (eg, lung abscess, bronchiectasis)
   Human immunodeficiency virus
   Subacute bacterial endocarditis
   Osteomyelitis
   Chronic urinary tract infections

2. Chronic inflammation
   Rheumatoid arthritis
   Systemic lupus erythematosus
   Inflammatory bowel disease
   Inflammatory osteoarthritis
   Gout
   Other (collagen vascular) diseases
   Chronic inflammatory liver diseases

3. Malignancies
   Carcinoma
   Lymphoma
   Leukemia
   Multiple myeloma

Anemia of Inflammation

Treatment:

- **The goals of therapy should include treating the underlying disorder and correcting reversible causes of anemia.**
- **Erythropoiesis-stimulating agent have been used for patients with anemia of inflammation, because a relative erythopoetin (EPO) deficiency exists.**

Anemia of Inflammation

Two agents are available:

1. **Recombinant epoetin alfa.**
2. **Recombinant darbepoetin alfa (has a longer half-life).**

- **Patients with chronic disease may have a relatively impaired response.**
- **Treatment is effective when the marrow has an adequate supply of iron, cobalamin, and folic acid.**

Anemia of Inflammation

Toxicities of erythropoetin administration:

- **Increases in blood pressure, nausea, headache, fever, bone pain, and fatigue.**
- **Less commonly, seizures, thrombotic events, allergic reactions (rashes), and local reactions at the injection site.**

Anemia of Inflammation

Monitoring of erythropoetin therapy:

- **Ensure the patient's Hb does NOT exceed 12 g/dL with treatment, or that Hb does NOT rise greater than 1 g/dL every 2 weeks.**
- **These cases have been associated with:**

➢ **increased mortality.**

➢ **cardiovascular events.**

➢ **tumor progression.**

Therapy of Osteoporosis

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Therapy of Osteoporosis

- **Osteoporosis is a bone disorder characterized by: low bone density, impaired bone architecture, and compromised bone strength, that predispose to an increased fracture risk.**
- **Osteoporosis is a major public health threat, with 55% of the people 50 years of age and older are expected to have this disease.**

Risk Factors of Osteoporosis

1. Female gender.
2. Advanced age.
3. Low body weight.
4. Systemic oral glucocorticoid therapy.
5. Cigarette smoking.
6. Alcohol (3 or more drinks/day).
7. Low calcium intake.
8. Low physical activity.
9. Vitamin D insufficiency and deficiency.
10. Others.

Medical Conditions Associated with Osteoporosis

1. Ovarian failure.
2. Testosterone deficiency.
3. Hyperthyroidism.
4. Cushing's syndrome.
5. Diabetes Mellitus.
6. Primary hyperparathyroidism
7. Anorexia nervosa.
8. Malabsorption.
9. Chronic liver disease and primary biliary cirrhosis.
10. Hypercalciuria.
11. Chronic kidney disease
12. Malignancies
13. Others.

Select Medications Associated with Increased Bone Loss and/or Fracture Risk

Drug	Comments
Anticonvulsant therapy (phenytoin, carbamazepine, phenobarbital)	↓ BMD and ↑ fracture risk; increased vitamin D metabolism leading to low 25(OH) vitamin D concentrations
Canagliflozin (sodium-glucose co-transport (SGLT-2) inhibitors)	↓ BMD and ↑ fracture risk
Furosemide	↑ fracture risk; increased calcium elimination by the kidney
Glucocorticoids (long-term oral therapy)	↓ BMD and ↑ fracture risk; increased bone resorption and decreased bone formation; Dose- and duration-dependent

BMD = bone mineral density

Select Medications Associated with Increased Bone Loss and/or Fracture Risk

Drug	Comments
Heparin (unfractionated, UFH) or low molecular weight heparin (LMWH)	↓ BMD and ↑ fracture risk (UFH >>> LMWH) with long-term use (> 6 months); decreased osteoblast formation and increased osteoclast function
Proton pump inhibitor therapy (long-term therapy)	↓ BMD and ↑ fracture risk; possible calcium malabsorption secondary to acid Suppression. (calcium, vitamin B12, iron & magnesium absorption may be reduced)
Selective serotonin reuptake inhibitors	↓ BMD and ↑ fracture risk; decreased osteoblast activity
Thiazolidinediones (pioglitazone and rosiglitazone)	↓ BMD and ↑ fracture risk; inhibit osteoblast differentiation and activate osteoclast differentiation
BMD = bone mineral density	

Prevention and Treatment

Desired Outcomes:

1. **The primary goal of osteoporosis care should be prevention.**
2. **Optimizing skeletal development and peak bone mass gain in childhood, adolescence, and early adulthood will reduce the future incidence of osteoporosis.**
3. **Once low bone mass or osteoporosis develops, the objective is to stabilize bone, improve bone strength and bone mass and prevent fractures.**

Prevention and Treatment

4. In patients who have already suffered osteoporotic fractures, reducing pain and deformity, improving functional capacity, improving quality of life, and reducing future falls and fractures are the main goals.

Prevention and Treatment

General approach to prevention and treatment:

A. **A bone-healthy life-style should begin at birth and continue throughout life: weight reduction, proper nutrition, moderation of alcohol intake, smoking cessation, exercise, and fall prevention.**

- **If employed early in life, it will help to optimize peak bone mass, and if continued throughout life it minimizes bone loss over time.**

Prevention and Treatment

B. **Adequate intake of calcium and vitamin D is the first step in prevention and treatment.**

C. **Prescription therapy is advised in any postmenopausal woman, or man age 50 years and older, presenting with a hip or vertebral fracture or low bone mass.**

Nonpharmacologic Therapy

Diet:

- **A diet well balanced in nutrients and minerals (without excessive protein) and limited use of salt, alcohol, and caffeine are important for bone health.**
- **Adequate amounts of calcium, vitamin D, and protein have documented impacts on bone health.**
- **Strontium (Sr) ranelate may be used for prevention of osteoporosis. It both increases deposition of new bone by osteoblasts and reduces the resorption of bone by osteoclasts.**

Nonpharmacologic Therapy

- **Being thin or having anorexia nervosa decrease bone mass.**

Calcium:

- **Adequate calcium intake is necessary for calcium homeostasis throughout life, bone development during growth, and bone maintenance.**
- **Dairy products have the highest amount of calcium per serving and are available in low-fat options.**

Nonpharmacologic Therapy

- **Carbohydrates, fat, and lactose increase calcium absorption whereas fiber, wheat bran, phytates (beans), oxylates (spinach), high-protein diets, caffeine, and smoking decrease absorption.**
- **When diet is NOT associated with adequate intake of calcium, calcium supplements are required.**

Nonpharmacologic Therapy

Vitamin D:

- **The 3 main sources of vitamin D are sunlight (cholecalciferol and vitamin D_3), diet, and supplements.**
- **Vitamin D_3 and D_2 come from oily fish, eggs, fortified dairy products.**
- **Inadequate concentrations of 25(OH) vitamin D are common.**

Nonpharmacologic Therapy

- **Low vitamin D concentrations result from insufficient intake, dietary fat malabsorption, decreased sun exposure, decreased skin production, or decreased liver and renal metabolism of vitamin D (may be genetically determined).**
- **Endogenous synthesis of vitamin D can be decreased by Sunscreen use.**
- **Darkly pigmented skin can decrease vitamin D production.**

Nonpharmacologic Therapy

- **Seasonal variations in vitamin D concentrations are seen with troughs in late winter and peaks in late summer.**
- **Because few foods are naturally high or fortified with vitamin D, most people, especially older adults, require supplementation.**

Nonpharmacologic Therapy

Alcohol:

- **Excessive alcohol consumption increases the risk for osteoporosis and fractures.**
- **It increases bone resorption and decreases bone formation by inhibiting signaling pathways and increasing oxidative stress that results in osteoblast apoptosis.**
- **Alcoholics may have poor nutrition, decreased calcium absorption, altered vitamin D metabolism, and impaired balance resulting in falls and fractures.**

Nonpharmacologic Therapy

Caffeine (?):

- **Although results are conflicting, excessive caffeine consumption may be associated with increased calcium excretion, increased rates of bone loss, and a modestly increased risk for fracture.**

Nonpharmacologic Therapy

Smoking:

- **Smoking cessation helps to optimize peak bone mass, minimize bone loss, and reduce fracture risk.**
- **The effect is dose- and duration-dependent, but even passive smoking shows adverse effects on BMD.**
- **It reduces intestinal calcium absorption.**
- **It increases 25(OH) vitamin D catabolism.**

Nonpharmacologic Therapy

Exercise:

- **It decreases the risk of falls and fractures by stabilizing bone density and improving muscle strength, coordination, balance, and mobility.**
- **Lack of physical activity can lead to suboptimal loading/straining, decreased stimulation of bone deposition, and a subsequently reduced peak bone mass.**

Nonpharmacologic Therapy

- **All patients who are medically fit should be encouraged to perform:**

A. a moderate-intensity weight-bearing activity (walking, jogging, golf, and stair climbing) daily.

B. a resistance activity (weight machines, free weights, or elastic bands).

Pharmacologic Therapy

Drug Treatments of First Choice:

- **Biphosphonates (alendronate, risedronate, zoledronic acid), combined with adequate calcium and vitamin D intake, or denosumab are the prescription medications of choice.**
- **This is based on evidence of reduction of the risk of hip and vertebral fractures.**
- **Ibandronate, teriparatide or raloxifene are alternatives and calcitonin is last-line therapy.**

Pharmacologic Therapy

- **Prescription therapy should be considered in any postmenopausal woman or man age 50 years and older presenting with osteoporosis or low bone mass with a significant probability of hip or any other osteoporosis-related fracture.**

Antiresorptive Therapies

Antiresorptive therapies include:

1. **Calcium**
2. **Vitamin D**
3. **Bisphosphonates**
4. **Estrogen agonists/antagonists (known previously as selective estrogen receptor modulators or SERMs)**
5. **Tissue selective estrogen complexes**
6. **Calcitonin**
7. **Denosumab**
8. **Estrogen**
9. **Testosterone**

Antiresorptive Therapies

Calcium Supplementation:

- **Adequate calcium intake is part of osteoporosis prevention and treatment.**
- **It should be combined with vitamin D, especially when osteoporosis medications are taken.**
- **It produces a small increase in BMD.**
- **It prevents fractures when combined with vitamin D.**

Antiresorptive Therapies

Adverse Effects:

1. **Constipation: can be treated with increased water intake, dietary fiber, and exercise.**
2. **Calcium carbonate can create gas and cause stomach upset. Calcium citrate has fewer GI adverse effects.**
3. **May increase kidney stones (?).**

- **Calcium intake should be less than 1500 mg daily, and preferably achieved through diet.**

Antiresorptive Therapies

Drug Interactions:

- **Proton pump inhibitors can decrease absorption from the carbonate product, because it requires acid for disintegration.**
- **Fiber laxatives can decrease the absorption of calcium if given concomitantly.**
- **Calcium can decrease the oral absorption of some drugs including iron, tetracyclines, quinolones, bisphosphonates, and thyroid supplements.**

Antiresorptive Therapies

Vitamin D Supplementation:

- **Vitamin D intake is critical for intestinal calcium absorption and when combined with calcium can prevent bone loss and decrease osteoporotic fractures.**
- **Vitamin D maintenances doses (800-2,000 units daily).**
- **Serum 25(OH) vitamin D is the best indicator of total body vitamin D status.**

Antiresorptive Therapies

Vitamin D ranges:

1. **30 to 100 ng/mL (sufficient)**
2. **20 and 29 ng/mL (insufficient)**
3. **< 20 ng/mL (deficient).**

- **Depend on the assay method and (??).**

Antiresorptive Therapies

Drug Interactions:

- **Some drugs can induce vitamin D metabolism: rifampin, phenytoin, barbiturates, and carbamazepine.**
- **Vitamin D absorption can be decreased by cholestyramine, colestipol, orlistat, and mineral oil.**
- **Vitamin D can enhance the absorption of aluminum; therefore aluminum-containing products should be avoided to prevent aluminum toxicity.**

Antiresorptive Therapies

Bisphosphonates:

- **Alendronate, risedronate, and intravenous zoledronic acid are indicated for postmenopausal females, males, and glucocorticoid-induced osteoporosis.**
- **Intravenous and oral ibandronate is indicated only for postmenopausal osteoporosis.**

Bisphosphonates

Pharmacology:

- **Are analogs of pyrophosphate in which the P-O-P bond is replaced by a nonhydrolyzable P-C-P bond.**
- **Bisphosphonates mimic pyrophosphate, an endogenous bone resorption inhibitor.**
- **They block prenylation and inhibit GTP-signaling proteins, which lead to decreased osteoclast maturation, number, recruitment, bone adhesion, and life span.**

Bisphosphonates

- **They retard formation and dissolution of hydroxyapatite crystals within and outside the skeletal system.**
- **They localize to regions of bone resorption and so exert their greatest effects on osteoclasts.**

Bisphosphonates

Efficacy:

- **Reduce fracture risk and increases BMD.**
- **The effect is dose-dependent and greatest in the first 12 months of therapy.**
- **Weekly alendronate, weekly and monthly risedronate, and monthly oral and quarterly intravenous ibandronate therapy produce equivalent BMD changes to their respective daily regimens.**
- **After discontinuation, the increased BMD is sustained for a prolonged period of time.**

Bisphosphonates

Adverse Effects:

1. **GI complaints: heartburn and dyspepsia, esophageal erosion and ulceration, GI bleeding.**

- **GI complaints are the most common reasons for discontinuing therapy.**
- **Switching to a different bisphosphonate or less frequent administration might resolve GI problems.**
- **Intravenous ibandronate and zoledronic acid can be used for patients with GI contraindications or intolerances to oral bisphosphonates.**

Bisphosphonates

2. **Injection reactions and musculoskeletal pain.**
- **If severe musculoskeletal pain occurs, the medication can be discontinued temporarily or permanently.**
3. **Acute phase reactions (fever, flu-like symptoms, myalgias, and arthralgias) are typically associated with intravenous administration, but rarely with daily, weekly or monthly oral bisphosphonates. This reaction usually diminishes with subsequent administration.**

Bisphosphonates

4. **Rarely, osteonecrosis of the jaw and atypical subtrochanteric femoral fractures.**

- **More commonly in patients with cancer, receiving higher-dose intravenous bisphosphonates, and glucocorticoids; and in those having diabetes mellitus.**
- **Risk factors include maxillary or mandibular bone surgery and poor oral hygiene.**

Bisphosphonates

Contraindications:

1. **Patients with creatinine clearances less than 30-35 mL/min.**
2. **Patients who have serious GI upset, peptic ulcer disease or esophageal motility disorders.**
3. **Patients who are pregnant should not take bisphosphonates.**

Bisphosphonates

Administration:

- **Each oral tablet should be taken with at least (~180 mL) of plain water (not coffee, juice, mineral water, or milk) at least 30 minutes (60 minutes for ibandronate) before consuming any food, supplements (calcium and vitamin D), or drugs.**
- **The patient should remain upright (either sitting or standing) for at least 30 minutes after alendronate and risedronate and 1 hour after ibandronate administration.**

Bisphosphonates

- **A patient who misses a weekly dose can take it the next day.**
- **If more than 1 day has lapsed, that dose is skipped until the next scheduled ingestion.**
- **If a patient misses a monthly dose: if the next month's dose is > 7 days away, take the missed dose on the morning you remember. Then resume your normal schedule. If the next dose is < 6 days away, wait until the next scheduled dose.**
- **Before intravenous bisphosphonates are used, the patient's serum calcium concentration must be normalized.**

Bisphosphonates

- **Creatinine clearance should be monitored before each dose of zoledronic acid.**
- **The intravenous products need to be administered by a healthcare provider.**
- **The quarterly ibandronate injection is given intravenously over 15 to 30 seconds.**
- **The injection can also be diluted with dextrose 5% in water or normal saline and used with a syringe pump.**

Bisphosphonates

- **Once-yearly administration of zoledronic acid should be infused over at least 15 minutes with a pump.**
- **Acetaminophen can be given to decrease acute phase reactions.**
- **Although these medications are effective, adherence is poor and results in decreased effectiveness.**

Bisphosphonates

- **A drug holiday could be considered in postmenopausal women after 5 years of oral bisphosphonates or 3 years of intravenous bisphosphonates.**
- **In women with a high fracture risk or lower hip BMD, continuing oral bisphosphonates for 10 years or intravenous bisphosphonates for 6 years should be considered (evidence on duration??).**
- **Other therapeutic uses include hypercalcemia associated with malignancy.**

Antiresorptive Therapies

Denosumab:

It is indicated for treatment of osteoporosis:

1) **in women and men at high risk of fractures.**
2) **to increase bone mass in men receiving androgen deprivation therapy [antiandrogens (flutamide), LHRH agonists (Leuprolide) for non-metastatic prostate cancer.**
3) **in women receiving adjuvant aromatase inhibitor therapy (anastrozole) for breast cancer who are at high risk of fractures.**

Antiresorptive Therapies

Pharmacology:

- **Denosumab is a fully human monoclonal antibody that binds to RANKL, blocking its ability to bind to its RANK (receptor activator of nuclear factor-κb) receptor on the surface of osteoclast precursor cells and mature osteoclasts.**
- **RANKL/RANK signaling regulates the formation of multinucleated osteoclasts from their precursors as well as their activation and survival in normal bone remodeling.**
- **Thus, it inhibits osteoclastogenesis and increases osteoclast apoptosis.**

Antiresorptive Therapies

- **Following subcutaneous injection, rapid suppression of bone turnover occurs within 12 hours.**

Pharmacokinetics:

- **Peak concentration is ~ 10 days.**
- **The half-life is ~ 25 days and the concentration slowly declines over a period of 4 to 5 months.**
- **The drug does NOT accumulate with repeated dosing at 6-month intervals.**
- **No dosage adjustment is necessary in renal impairment.**

Antiresorptive Therapies

Efficacy:

- **Over 3 years, it significantly decreased vertebral fractures, non-vertebral fractures, and hip fractures in postmenopausal women with low bone density.**
- **The BMD effects are at least similar to weekly alendronate, and can increase BMD in patients with prior alendronate therapy.**
- **Activity dissipates with drug discontinuation .**

Antiresorptive Therapies

Adverse Effects:

1. **Dermatitis, eczema, and rashes.**
2. **Bone turnover suppression.**
3. **Serious infections including skin infections.**
4. **Muscle, bone, and joint pain and atypical fractures.**
5. **Hypocalcemia (more common in severe renal impairment).**

Antiresorptive Therapies

- **Any existing hypocalcemia should be corrected prior to use with adequate calcium and vitamin D supplements.**
- **Monitoring of serum calcium, magnesium, and phosphorus is recommended within 14 days of administration in patients having a Cl_{Cr} < 30 mL/min.**

Antiresorptive Therapies

Mixed Estrogen Agonists/Antagonists:

Raloxifene:

- **is a second-generation mixed estrogen agonist/antagonist used for:**

1. **prevention and treatment of postmenopausal osteoporosis**
2. **reducing the risk of invasive breast cancer in postmenopausal women with and without osteoporosis.**

- **No benefit on cardiovascular disease.**

Antiresorptive Therapies

Pharmacology:

- **Raloxifene is an agonist at bone estrogen receptors and antagonist at breast estrogen receptors; it has minimal effect on the uterus.**
- **Bazedoxifene is an agonist at bone, and antagonist at the uterus and breast, with no breast cancer prevention effects.**
- **After raloxifene discontinuation, the effect is lost, with bone loss returning to age- or disease-related rates.**

Antiresorptive Therapies

Adverse Events:

1. **Hot flushes are common with raloxifene but not with bazedoxifene.**
2. **Raloxifene rarely causes endometrial thickening and bleeding; bazedoxifene decreases these adverse events.**
3. **Leg cramps and muscle spasms are also common.**
4. **Thromboembolic events are uncommon, but can be fatal.**

Antiresorptive Therapies

Potential Drug Interactions:

1. **Raloxifene is highly protein bound (95%), and may have binding interactions with highly protein bound drugs (warfarin).**
2. **Cholestyramine can decrease raloxifene absorption.**
3. **Rifampin, phenytoin, carbamazepine, and phenobarbital can decrease bazedoxifene levels by inducing intestinal and liver uridine diphosphate glucuronosyltransferases.**
4. **Estrogen metabolism is decreased with CYP3A4 inhibitors.**

Antiresorptive Therapies

Contraindications:

1. **active or history of venous thromboembolic disease.**
2. **pregnancy, or childbearing potential.**
3. **known coronary artery disease.**
4. **peripheral vascular disease.**
5. **atrial fibrillation.**
6. **prior history of cerebrovascular accidents.**

Anabolic Therapies

Teriparatide:

- **It is a recombinant human product representing the first 34 amino acids in human PTH.**
- **It increases bone formation, bone remodeling rate, and osteoblast number and activity.**
- **It inhibits osteoblast apoptosis.**
- **Both bone mass and architecture are improved.**

Anabolic Therapies

Indications:

1. **Postmenopausal women at high risk of fractures.**
2. **Men with idiopathic or hypogonadal osteoporosis at high risk of fractures.**
3. **Men or women intolerant to other osteoporosis medications.**
4. **Patients with glucocorticoid-induced osteoporosis.**
5. **Patients who have a history of osteoporotic fracture, multiple risk factors for fracture, very low bone density, or have failed or are intolerant of previous bisphosphonate therapy.**

Anabolic Therapies

- **Discontinuation of teriparatide therapy results in a decrease in BMD.**

Administration:

- **Daily subcutaneous injection with site rotation.**
- **The administration of the first dose should take place with the patient either sitting or lying down to avoid orthostatic hypotension.**
- **Duration of therapy is 18 to 24 months.**

Anabolic Therapies

Adverse Effects:

- **Transient and rare hypercalcemia (avoid in patients having hypercalcemia).**
- **May predispose to osteosarcoma (seen in lab animals).**
- **Avoid in Paget's bone disease, unexplained elevations of alkaline phosphatase, patients with open epiphyses, or patients with prior radiation therapy involving the skeleton.**

Glucocorticoid-Induced Osteoporosis

- **Current and prior glucocorticoid use is the most common cause of drug-induced osteoporosis.**
- **Trabecular bone is affected more than cortical bone.**
- **The pathophysiology of glucocorticoid bone loss is multifactorial:**

1. **They decrease bone formation through decreased proliferation and differentiation and enhanced apoptosis of osteoblasts.**
2. **They increase apoptosis of osteocytes.**

Glucocorticoid-Induced Osteoporosis

3. They increase bone resorption by increasing RANKL.
4. They can reduce estrogen and testosterone concentrations.
5. Negative calcium balance: decreased calcium absorption and increased urinary calcium excretion via alterations in calcium transporters.
6. The underlying disease requiring this medication also can affect bone metabolism negatively.

Glucocorticoid-Induced Osteoporosis

- **All patients using glucocorticoids should practice a bone-healthy lifestyle.**
- **All patients starting or receiving glucocorticoid therapy (any dose or duration) should ingest 1,200 to 1,500 mg elemental calcium and 800 to 1,200 units of vitamin D daily or more to achieve therapeutic 25-(OH) VD concentration.**
- **Glucocorticoids should be used at the lowest dose and for the shortest duration possible.**
- **After discontinuation, fracture risk is still higher than never users.**

Glucocorticoid-Induced Osteoporosis

Treatment:

- **Alendronate, risedronate, zoledronic acid, and teriparatide can be used.**
- **Raloxifene and denosumab may decrease bone loss from glucocorticoids.**
- **Bisphosphonate drug holiday is generally NOT considered in this condition.**

Therapy of Gout and Hyperuricemia

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Introduction

Gout describes a heterogeneous clinical spectrum of diseases including:

1. **Elevated serum urate concentration (hyperuricemia).**
2. **Recurrent attacks of acute arthritis associated with:**

a. **monosodium urate (MSU) crystals in synovial fluid leukocytes.**

b. **deposits of monosodium urate crystals (tophi) in tissues in and around joints.**

c. **interstitial renal disease.**

d. **uric acid nephrolithiasis.**

Introduction

- **The underlying metabolic disorder of gout is hyperuricemia, defined as serum that is supersaturated with monosodium urate.**
- **At 37°C, serum urate concentrations around 7 mg/dL begin to exceed the limit of solubility for monosodium urate.**
- **Elevated serum urate level is the single most important risk factor for the development of gout.**

Introduction

- **Hyperuricemia does NOT always lead to gout, and many patients with hyperuricemia remain asymptomatic.**
- **Another major contributor to the increased prevalence of gout is obesity.**
- **Dietary and life-style factors linked to obesity (consumption of alcohol, sugary beverages, and red meat; along with a sedentary life-style) may be associated with gout.**

Introduction

- **Uric acid is produced from purines ← increased breakdown of tissue nucleic acids:**

1. **Starvation.**
2. **Chronic hemolytic anemias.**
3. **Toxemia of pregnancy.**
4. **Obesity.**
5. **Acute alcoholism.**
6. **Psoriasis.**

Introduction

7. **Myeloproliferative and lymphoproliferative disorders.**
8. **Polycythemia vera.**
9. **Cytotoxic drugs use can result in overproduction of uric acid secondary to lysis and breakdown of cells.**

Introduction

Acute Gouty Arthritis:

- **Acute inflammatory mono-arthritis.**
- **The first metatarsophalangeal joint is often involved.**
- **Any joint of the lower extremity, wrist or fingers can be affected.**
- **Gout may include: nephrolithiasis, gouty nephropathy, and aggregated deposits of sodium urate (tophi) in cartilage, tendons, synovial membranes, etc.**

Introduction

- **Acute attacks of gout can be precipitated by a rapid change in serum uric acid levels, either rapid increase or rapid decrease.**
- **When serum uric acid level is rapidly decreased by uric acid lowering agent, dissolution of tophi takes place which will increase serum uric acid levels.**

Introduction

- **~ 90% of filtered uric acid is reabsorbed in the proximal tubule, by both passive and active transport mechanisms.**
- **Proximal tubular sodium reabsorption and uric acid reabsorption are linked, so that conditions that enhance sodium reabsorption (dehydration) lead to increased uric acid reabsorption. (Co-transport)**
- **Uric acid is also secreted in the tubules by an active transport process.**

Drug-Induced Hyperuricemia

Drugs capable of inducing hyperuricemia and gout:

1. **Diuretics.**
2. **Nicotinic acid.**
3. **Ethanol.**
4. **Pyrazinamide.**
5. **Levodopa.**
6. **Ethambutol.**

Drug-Induced Hyperuricemia

7. **Cytotoxic drugs.**
8. **Cyclosporine.**
9. **Salicylates:**

a) **At < 2g/day, salicylates block the active secreting system of uric acid leading to uric acid retention.**

b) **At > 2.5g/day, salicylates are uricosuric by blocking active uric acid reabsorption.**

- **Insulin resistance may be associated with gout, by enhancing renal urate reabsorption.**

Therapy of Gout and Hyperuricemia

The goals of treatment of gout:

1. **To terminate the acute attack.**
2. **To prevent recurrence of attacks.**
3. **To prevent complications associated with chronic deposition of urate crystals in tissues.**

- **These goals can be accomplished through a combination of pharmacologic and nonpharmacologic methods, including focused patient education.**

Acute Gouty Arthritis

Therapy:

- **For most patients, acute attacks of gouty arthritis may be treated successfully with:**

1. **Nonsteroidal anti-inflammatory drugs (NSAIDs).**
2. **Corticosteroids.**
3. **Colchicine.**

- **All are considered first-line monotherapy for the treatment of acute gout.**

Acute Gouty Arthritis

- **Treatment should be started within 24 hours of the onset of an attack, and continued until complete resolution.**
- **Combination drug therapy is indicated in:**

1. **More severe cases.**
2. **Multiple joints involvement.**
3. **High intensity pain.**

Acute Gouty Arthritis

NSAIDs:

- **NSAIDs are a mainstay of therapy for acute attacks of gouty arthritis - excellent efficacy and minimal toxicity with short-term use.**
- **Following resolution of the attack, NSAID therapy may be tapered, especially in patients with hepatic or renal insufficiency. (to prevent rebound)**
- **Resolution of an acute attack takes 5-8 days after initiating therapy.**

Acute Gouty Arthritis

Adverse effects:

1. **GI: gastritis, bleeding, perforation.**
2. **Kidney: renal papillary necrosis, reduced creatinine clearance (renal dysfunction).**
3. **Cardiovascular system: sodium and water retention, increased blood pressure.**
4. **CNS: impaired cognitive function, headache, dizziness.**

- **etc**

Acute Gouty Arthritis

- **Should be use with caution in patients with a history of peptic ulcer disease, congestive heart failure, uncontrolled hypertension, renal insufficiency, coronary artery disease, or who are concurrently receiving anticoagulants or antiplatelet drugs.**
- **Some of the choices include but are NOT limited to indomethacin, naproxen, and sulindac.**
- **Selective cyclooxygenase-2 (COX-2) inhibitors are better tolerated in patients with GI problems, but have higher cardiovascular risk. (Celecoxib, etoricoxib and lumiracoxib are options).**

Acute Gouty Arthritis

Corticosteroids:

- **Corticosteroids are equivalent to NSAIDs in the treatment of acute gout flares.**
- **They can be used either systemically or by intra-articular injection, depending on the number of joints involved.**
- **Should be tapered gradually to avoid rebound.**
- **Prednisone, prednisolone, and methylprednisolone are some options for systemic use, and triamcinolone acetonide for intra-articular injections.**

Acute Gouty Arthritis

Adverse effects:

- **Are generally dose- and duration-dependent.**
- **Short-term use for treatment of acute attacks is generally well tolerated.**
- **Increase blood sugar.**
- **Monitor patients with a history of GI problems, bleeding disorders, cardiovascular disease, and psychiatric disorders.**
- **Long-term corticosteroid use should be avoided because of the risk for osteoporosis, hypothalamic–pituitary-adrenal axis suppression, and cataracts.**
- **etc…**

Acute Gouty Arthritis

Colchicine:

- **Colchicine is an antimitotic drug that is highly effective at relieving acute attacks of gout.**
- **When started within the first 24 hours of an acute attack, it produces a response within hours of administration.**
- **Should be started within 36 hours of attack.**
- **Delayed initiation of colchicine is associated with substantial reduction of response.**

Acute Gouty Arthritis

Adverse effects:

- **Dose-dependent GI adverse effects: nausea, vomiting, and diarrhea.**
- **Neutropenia and axonal neuromyopathy, worsened in patients taking statins, or in those with renal insufficiency.**
- **Concurrent administeration with P-glycoprotein or cytochrome P450 3A4 inhibitors (clarithromycin or cyclosporine), increases colchicine concentration.**
- **Use with caution inpatients with renal and hepatic dysfunction.**

Hyperuricemia in Gout

Nonpharmacologic Therapy:

- **Recurrent gout attacks can be prevented by maintaining low uric acid levels.**
- **Patient education is a critical first step in the management of hyperuricemia.**

Lifestyle/Dietary modification:

1. **Weight loss and exercise may enhance renal excretion of urate.**

Hyperuricemia in Gout

2. **Restriction of alcohol intake because alcohol reduces renal urate excretion.**
- **Long-term alcohol intake increases production of purines as a by-product of the conversion of acetate to acetyl coenzyme-A in the metabolism of alcohol.**
3. **Encourage the consumption of vegetables and low-fat dairy products, which lower urates.**

Hyperuricemia in Gout

4. Reduce consumption of high-fructose diet, and purine-rich foods (organ meats and some seafood), which cause uric acid elevation.
5. Avoid (if possible) drugs that may elevate uric acid levels:

a. Thiazide and loop diuretics.
b. Calcineurin inhibitors.
c. Niacin.
d. Low-dose aspirin.

Hyperuricemia in Gout

- **Thiazide diuretics and Low-dose aspirin are useful in treating hypertension and cardio-protection, respectively.**

Hyperuricemia in Gout

Pharmacologic Therapy:

- **After the first attack of acute gouty arthritis, consider prophylactic use of uric acid-lowering drugs.**
- **(Antiinflamatory drugs prevent attacks only).**

Other indications for lowering uric acid include:

1) **the presence of tophi.**
2) **chronic kidney disease (stage 2 or worse).**
3) **history of urolithiasis.**
4) **Cancer chemotherapy.**

Hyperuricemia in Gout

- **Uric acid-lowering therapy should be long-term.**
- **Reduction of serum uric acid concentrations can be accomplished pharmacologically by:**

a. **decreasing the synthesis of uric acid (xanthine oxidase inhibitors)**
b. **increasing the renal excretion of uric acid (uricosuric agents).**

Hyperuricemia in Gout

- **Xanthine oxidase inhibitors are first-line therapy.**
- **Probenecid, a potent uricosuric, is an alternative in patients with a contraindication or intolerance to xanthine oxidase inhibitors.**

Hyperuricemia in Gout

Xanthine Oxidase Inhibitors:

- **Impair the conversion of hypoxanthine to xanthine and xanthine to uric acid.**
- **Effective in over-producers of uric acid, as well as in those with low excretion.**

Allopurinol:

- **It is an effective uric acid-lowering agent, but long-term adherence is low.**

Hyperuricemia in Gout

Adverse effects:

- **Mild-moderate adverse effects: skin rash, leukopenia, GI disturbances, headache, and urticaria.**
- **More severe adverse reactions including severe rash (toxic epidermal necrolysis, erythema multiforme, or exfoliative dermatitis), hepatitis, interstitial nephritis, and eosinophilia. These adverse effects are associated with a 20-25% mortality.**

Hyperuricemia in Gout

Febuxostat:

- **Similar to allopurinol, but newer drug.**

Adverse effects:

- **Nausea, arthralgias, and minor hepatic transaminases elevation.**
- **An advantage of febuxostat is that it does not require dose adjustment in patients with moderate hepatic and renal impairment.**

Hyperuricemia in Gout

Uricosuric Drugs:

- They increase the renal excretion of uric acid by inhibiting its proximal tubular reabsorption.
- The drug used most widely is probenecid.
- Uricosuric drugs cause marked uricosuria and may cause uric acid stone formation.
- The maintenance of adequate urine flow and alkalinization of the urine may reduce uric acid nephrolithiasis.

Hyperuricemia in Gout

- **Other major adverse effects include GI irritation and precipitation of acute gouty arthritis.**
- **Salicylates at low dose ranges may interfere with their mechanism and result in treatment failure.**
- **Probenecid can inhibit the tubular secretion of other organic acids and increase plasma concentrations of penicillins, cephalosporins, sulfonamides, and indomethacin.**

Hyperuricemia in Gout

Uricosuric drugs are contraindicated in patients:

1. **allergic to them.**
2. **with impaired renal function (a creatinine clearance less than 50 mL/min).**
3. **who are overproducers of uric acid. (for such patients, a xanthine oxidase inhibitor should be used).**

Hyperuricemia in Gout

Lesinurad:

- **It is a selective uric acid reabsorption inhibitor (SURI).**
- **It inhibits urate transporter 1 (URAT1), a transporter found in the proximal renal tubules, resulting in uric acid excretion.**

Adverse effects:

1. **Increased serum creatinine, elevated lipase, increased creatine kinase, and urticaria.**

Hyperuricemia in Gout

2. Acute renal failure.

- **It should not be used in patients with creatinine clearance less than 45 mL/min.**
- **May be used in a combination with a xanthine oxidase inhibitor for treatment of hyperuricemia in patients who have not achieved target serum uric acid levels with xanthine oxidase inhibitor monotherapy.**

Hyperuricemia in Gout

3. Headache, flu-like symptoms.
4. Gastroesophageal reflux disease (GERD).
5. Kidney stones.

Hyperuricemia in Gout

Pegloticase:

- **It is a pegylated recombinant uricase that reduces serum uric acid by converting uric acid to allantoin, a water-soluble and easily excretable compound.**
- **It is effective in reducing serum uric acid and resolving tophi in patients with severe gout and hyperuricemia who failed or had a contraindication to allopurinol therapy.**

Hyperuricemia in Gout

- **Severe gout has at least one of the following criteria:**

1. **three or more gout flares within the last 18 months.**
2. **one or more tophi.**
3. **joint damage due to gout.**

- **Given as bi-weekly IV infusions over no less than 2 hours, which may NOT be convenient.**

Hyperuricemia in Gout

- May be associated with infusion-related allergic reactions, and patients must be pre-treated with antihistamines and corticosteroids before therapy.
- Duration of therapy is unknown.
- Immunogenic and leads to development of pegloticase antibodies.
- An agent of last resort that should be reserved for patients with refractory hyperuricemia with gout.

Anti-Inflammatory Gout Prophylaxis during Urate-Lowering Therapy (ULT)

- **Initiation of ULT can prompt an acute attack of gout due to remodeling of urate crystal deposits in joints as a result of rapid lowering of urate concentrations.**
- **Thus, prophylactic antiinflammatory therapy is recommended to prevent gout attacks.**
- **Low-dose oral colchicine and low-dose NSAIDs are first-line prophylactic therapies, with stronger evidence supporting use of colchicine.**

Anti-Inflammatory Gout Prophylaxis during Urate-Lowering Therapy (ULT)

- **Low-dose corticosteroid therapy is an alternative in patients with intolerance, contraindication, or lack of response to first-line therapy.**
- **Continue prophylaxis for at least 3 months after achieving target serum uric acid or 6 months total, whichever is longer.**
- **For patients with one or more tophi, prophylactic therapy should be continued for 6 months following achievement of serum urate target.**

Urate Nephrolithiasis

- **Treatment by life-style modification mentioned earlier.**
- **Hydration to maintain a urine volume of 2 to 3 L/day.**
- **Reduction of urinary uric acid excretion.**
- **Alkalinization of urine. Urine pH should be maintained at 6-6.5, by the administration of potassium bicarbonate or potassium citrate.**

  (At a urine pH of 6.75, > 90% of the total urinary uric acid will be as more soluble urate salt).

Urate Nephrolithiasis

- **Administration of alkali with sodium salts should be avoided for two reasons:**

1. **The sodium-induced volume expansion will increase sodium excretion, which can lead to proximal Na reabsorption.**
- **Such a mechanism may be associated with secondary calcium reabsorption with sodium, leading to hypercalcemia. This can lead to calcium oxalate stone formation.**

Urate Nephrolithiasis

2. **Older patients with uric acid kidney stones may also have hypertension, congestive heart failure, or renal insufficiency. Overload with alkalinizing sodium salts or unlimited fluid intake can worsen these conditions.**

- **Acetazolamide produces rapid and effective urinary alkalinization.**

Urate Nephrolithiasis

- **The mainstay of drug therapy for recurrent uric acid nephrolithiasis is xanthine oxidase inhibitors.**
- **They are also recommended as prophylactic treatment for patients who will receive cytotoxic agents for the treatment of lymphoma or leukemia.**