DRUG INTERACTIONS

DEFINITION

- A drug interaction is defined as the "pharmacologic or clinical response to the administration of a drug combination different from that anticipated from the known effects of the two agents."
- The interaction may result in a change in the nature or type of response to a drug (i.e., *pharmacodynamic* interaction), or a change in the magnitude or duration of response to a drug (i.e., *pharmacokinetic* interaction).
- Most commonly, a drug interaction is taken to mean an interaction between two or more medicines, which is a drug–drug interaction.
- However, a "drug interaction" can have many causes.
- For example, several food–drug interactions have been well documented, and within this category, enteral feeding–drug interactions, nutrient–drug interactions, alcohol–drug interactions, and tobacco–drug interactions are all well established.
- With the rising use of alternative medicines, herbal– or botanical–drug interactions are increasingly being reported.
- Furthermore, drug–disease interactions, drug–laboratory interactions, and parenteral–drug interactions may result in physical and chemical incompatibility.

EPIDEMIOLOGY

- In 2004 in the United States, more than 3,500 drugs could be prescribed, and any five of these drugs could be used in 5.2×10^{17} different combinations.
- When the large number of alternative medicines (e.g., herbs, botanicals), vitamins, and foods with pharmacologically active ingredients (e.g., caffeinated beverages, calcium-fortified drinks, herbal teas, "naturally" fortified beverages) that are available are factored into this, the number of possible combinations is even more staggering.
- A review of drug usage in the United States found that more than 81% of persons in a given week take at least one medication [prescription drug, over-the-counter (OTC) product, vitamin, mineral, or herbal supplement], and 25% take at least five such medications.
- Clearly, the *potential* for an interaction between two or more agents is large.
- The reported frequency of drug interactions varies greatly depending upon the population studied (outpatients vs. hospitalized patients vs. nursing home residents), the type of interaction reported (any interaction vs. only interactions that cause an adverse event), the study design (prospective vs. retrospective), and the demographics of the population studied (e.g., elderly vs. young patients).

- The Boston Collaborative Drug Surveillance program reported 83,200 drug exposures in almost 10,000 patients and found 3,600 adverse drug reactions, of which 6.5% resulted from drug interactions.
- A review of the adverse event literature in 1993 found that up to 2.8% of hospitalizations resulted from drug–drug interactions: another study found almost double that rate in Australian hospitals.
- A US study found that drug–drug interactions accounted for 4.6% of adverse events *during* hospitalization, and a recent literature review reported that 2.8% of preventable adverse drug events in the hospitalized population were due to drug–drug interactions.
- A recent study of medication use by residents of three nursing homes found drug interactions with 5.8% of all drugs being taken.
- The occurrence of drug–drug interactions in the ambulatory setting is reported to be as high as 70.3%.
- However, a recent study that applied successive filters to screen out inconsequential drug combinations found that clinically relevant interactions occurred in only 0.04% of ambulatory patients.
- Finally, in a retrospective review of adverse event reports, it was noted that drug interactions accounted for 10.5% of all drug-related events that would likely result in patient death if no intervention was made.

RISK FACTORS OF DRUG INTERACTION

- A high degree of variability has been observed in patient response to two or more interacting compounds.
- Plainly put, not every patient reacts the same way or to the same degree when exposed to the same interacting drugs.
- Several factors, both patient specific and drug specific, influence the risk of drug interactions.
- Intuitively, it has been noted that the risk of drug interaction increases as the number of pharmacologically active compounds used increases.
- A retrospective study of patients who presented to two emergency departments found that significant drug interactions increased from 34% among patients taking two medications to 82% in patients taking seven or more medicines.
- Use of multiple prescribers and/or multiple pharmacies increases the odds that health professionals will have incomplete medical and drug information available to them, and raises the chance that a potential drug interaction may go undetected.
- The genetic makeup of an individual determines his or her complement of metabolizing enzymes and other proteins.
- Patients classified as slow metabolizers appear to be at less risk for drug interactions than extensive metabolizers or ultrarapid metabolizers.

- Specific populations are at increased risk of experiencing drug interactions.
- For example, the elderly, because of a greater number of chronic illnesses, increased drug usage to manage those illnesses, and age-related physiologic changes (e.g., decreased renal function, decreased protein binding), are at higher risk for drug interactions and adverse events.
- A number of studies have found females to be at greater risk for drug interactions.
- Obese patients have altered levels of metabolizing enzymes, making them more susceptible to drug interactions, as do malnourished patients.
- Other populations at risk include critically ill patients, patients with autoimmune disorders, and transplant recipients.
- Drugs with a narrow therapeutic index, a steep dose-response curve, or potent pharmacologic effects have been associated with greatest risk for significant drug interactions.
- Aminoglycosides, cyclosporine, some medicines for human immunodeficiency virus (HIV), many anticonvulsants, many antiarrhythmics, and anticoagulants fall into this category.
- Several diseases seem to predispose patients to drug interactions.
- This is due to a combination of factors. For example, some disease states such as congestive heart failure, acquired immunodeficiency syndrome (AIDS), epilepsy, or psychiatric illness may require multiple medications for effective management.
- Many of the drugs used to treat some illnesses, such as tuberculosis, epilepsy, and AIDS, are potent enzyme inducers or inhibitors and therefore predispose patients to drug interactions.
- Some illnesses are treated with a narrow therapeutic index drug. Lithium, used for bipolar disorder, has a very narrow therapeutic range, for instance.
- Consequently, even minor changes in its blood level caused by a drug interaction could lead to toxicity.
- Finally, many drug interactions are concentration dependent.
- Thus, the occurrence of the interaction and its outcome are often dictated by the dose of the drug and its pharmacokinetics.

Risk Factors for Drug Interactions
Polypharmacy
Multiple prescribers
Multiple pharmacies
Genetic makeup
Specific populations • Females • Elderly • Obese • Malnourished • Critically ill patients • Transplant recipients
Specific illnesses • Cardiovascular disease (CHF, arrhythmias) • Diabetes • Epilepsy • Gastric illness (ulcer disease, dyspepsia) • Hepatic disease • Hyperlipidemia • Hypothyroidism • Infection (HIV, fungal infection) • Psychiatric illness • Renal dysfunction • Respiratory illness (asthma, COPD)
Drug dose
Narrow therapeutic index drugs • Aminoglycosides • Antiarrhythmics (quinidine, lidocaine, procainamide) • Carbamazepine • Cyclosporine • Digoxin • Insulin • Lithium • Oral sulfonylureas • Phenytoin • Theophylline • Tricyclic antidepressants • Unfractionated heparin • Valproic acid • Warfarin

ETIOLOGY

PHARMACOKINETICS

Most drug interactions are pharmacokinetic in nature, that is, the perpetrator drug affects the absorption, distribution, metabolism, or excretion of the object drug.

- **ABSORPTION**
  - ✓ After oral administration, most drug absorption takes place in the proximal small intestine, where the large surface area facilitates this process.
  - ✓ However, drug interactions that alter absorption may occur throughout the GI tract through a variety of mechanisms, including **complexation** (adsorption or chelation), **changes in pH**, and **changes in GI motility**, **altered drug transport**, and **enzymatic metabolism**.
  - ✓ The net effect of one or more of these processes is a change in the *rate* of drug absorption, or a change in the *extent* of drug absorption.
  - ✓ In the former situation, the total amount of drug absorbed remains the same, only the speed with which it is absorbed is changed.
  - ✓ **Complexation**
    - o Agents that form chemical complexes with drugs may cause lower rates of drug absorption.
    - o Cholestyramine or colestipol lowers cholesterol by binding bile acids in the intestine, inhibiting their reabsorption and enterohepatic recirculation, and increasing their fecal excretion.
    - o This same action affects numerous drugs when they are coadministered with one of these bile acid–binding resins, including digoxin, warfarin, levothyroxine, furosemide, and mycophenolate.
    - o The result is lowered serum concentration and reduced effectiveness.
    - o Divalent and trivalent metallic ions such as magnesium, aluminum, calcium, zinc, bismuth, and iron can form insoluble complexes with drugs, also resulting in reduced serum levels and possibly therapeutic failure.
    - o The quinolone antibiotics are highly susceptible to chelation by sucralfate, most antacids, calcium acetate, and ferrous sulfate (including iron in multivitamins), as are many of the tetracycline antibiotics and penicillamine.
    - o The bisphosphonates alendronate and risedronate are rendered ineffective if taken with any calcium-containing compound.

- ✓ **Gastric Acidity**
  - Some drugs, for example, ketoconazole, itraconazole, atazanavir, and iron supplements, require an acidic environment for optimal dissolution and absorption.
  - Compounds that raise gastric pH such as H_2 receptor blockers (e.g., cimetidine, ranitidine), proton pump inhibitors (e.g., omeprazole, lansoprazole), or antacids can reduce the absorption of these drugs, thereby decreasing their effectiveness.
- ✓ **Gastric Motility**
  - Many drugs alter gastrointestinal motility. For example, narcotics or drugs with anticholinergic effects (e.g., tricyclic antidepressants, phenothiazines, oxybutynin, tolterodine) can slow GI motility.
  - On the other hand, metoclopramide, erythromycin, and some laxatives can increase GI motility.
  - How altered GI motility affects drug absorption is difficult to predict, however. Slowing motility may lead to enhanced drug absorption by allowing more time for drug dissolution and prolonged contact with the absorptive surface of the small intestine.
  - Alternatively, slowed motility may prolong exposure to intestinal enzymes, reducing the amount of drug available for absorption.
  - Enhanced motility may speed the transit of drugs through the GI tract, decreasing medication absorption.
  - This is particularly important for drugs that require prolonged contact with the absorptive surface, or those drugs that have an "absorption window."
  - Sustained-release products and enteric-coated drugs may also undergo decreased absorption if GI motility is increased.
- ✓ **Altered Drug Transport**
  - Two types of transport proteins are present in the intestinal mucosa—those that are involved in the transport of compounds from the lumen of the intestine into the portal bloodstream, and those that are involved in the efflux of compounds from the intestinal mucosa back into the gut lumen.
  - Of these, efflux transporters, particularly P- glycoprotein (Pgp), are the most studied and are a source of drug interactions.
  - Pgp is located on the apical surface of mucosal cells in the intestine, generally in increasing concentration from the stomach to the colon, and is oriented to pump compounds from the inside of the cell back into the gut lumen.

- Several drugs are substrates of Pgp, meaning that these drugs are normally transported from intestinal cells back into the intestinal lumen after oral administration.
- Also, several drugs are now known to block the action of Pgp (i.e., they are Pgp inhibitors).
- Coadministration of a Pgp substrate and an inhibitor increases the amount of substrate available for absorption and may elevate the serum drug concentration.
- Similarly, some compounds such as rifampin are known to increase expression of Pgp.
- Administration of a substrate with a Pgp inducer leads to enhanced efflux of the substrate into the gut lumen, and lower serum levels of the substrate.

✓ **Intestinal Metabolism**

- The intestinal mucosa is now appreciated to be much more than an organ for passive drug diffusion.
- As has been stated, many phase I and phase II enzymes are present in the small and large intestines, conferring the gastrointestinal mucosal a significant role in drug metabolism and the first-pass effect.
- The highest concentration of mucosal enzymes is found in the duodenum, followed by the jejunum, ileum, and colon.
- CYPs 1A1, 2C, 2D6, and 3A4 have been identified in the human small intestine; of these, CYP3A4 is the most prevalent oxidative enzyme and the most important.
- In most individuals, the amount of CYP3A4 in the intestine is 10% to 50% lower than that found in the liver, although exceptions have been documented.
- Thus, drugs that are substrates of CYP3A4 can undergo significant metabolism in the small intestine during cellular transport before ever reaching the hepatic circulation.
- It is important to note that CYP3A4 and Pgp have similar areas of distribution along the GI tract, and most substrates of Pgp are CYP3A4 substrates as well, suggesting a cooperative role in drug metabolism.
- This model is supported at the molecular level by the recognition that the nuclear receptor, SXR, synchronizes transcription of both CYP3A4 and Pgp.
- For example, a compound (also called a *ligand*) such as phenobarbital binds to the SXR receptor and stimulates transcription of both CYP3A4 and Pgp coordinately.

- A system of "intestinal recycling" is proposed, wherein drug diffuses into the intestinal cell and is then secreted by Pgp back into the gut lumen; this process is followed by oxidation by CYP3A4.
- The process of diffusion, extrusion, and metabolism is repeated as the drug travels along the GI tract.
- The net effect is an increase in the intracellular residence time of the drug, a decrease in its rate of absorption, and increased drug metabolism relative to crossing of the intestine by the unmetabolized drug.
- Inhibitors of CYP3A4 will interfere with the metabolism of drugs that are CYP3A4 substrates, resulting in greater absorption and elevated serum levels.
- On the other hand, a CYP3A4 inducer will increase enzyme activity, causing increased metabolism of CYP3A4 substrates and lower serum levels.
- Just as CYP3A4 and Pgp have common substrates, they also have common inhibitors (e.g., erythromycin, ketoconazole) and inducers (e.g., rifampin).
- Administration of a drug that is a substrate of both CYP3A4 and Pgp with another drug that is an inhibitor of both can lead to a significant increase in plasma levels, in that the efflux action of Pgp is blocked (i.e., more drug is absorbed by the intestinal mucosa) and the metabolic ability of CYP3A4 is reduced (allowing more unmetabolized drug to be absorbed).
- The exact opposite occurs when a Pgp/3A4 substrate is administered with an inducer of both, that is, significantly reduced plasma levels of drug are observed.

- **DISTRIBUTION**
  - ✓ **Protein Displacement**
    - Following administration and absorption, drugs are quickly distributed throughout the body.
    - Some drugs have near-complete dissolution in the plasma, but many are bound to circulating proteins—acidic drugs generally to albumin and basic drugs to α_1-glycoprotein.
    - The degree of protein binding is variable, ranging from less than 10% to 99% or greater.
    - Regardless of the extent of protein binding, equilibrium is established between bound and unbound drug, and it is only the unbound or free fraction of the drug that is capable of exerting a pharmacologic effect.

- Competition between drugs for the same protein-binding site can lead to displacement of bound drug and an increase in its unbound or free fraction.
- Displacement occurs only if both drugs are highly protein bound (>90%). Such drug interactions, however, most often are not clinically meaningful for several reasons.
- First, following displacement, the free fraction of the drug rises, transiently increasing its serum level and possibly its pharmacologic action.
- However, the newly unbound drug is also available for distribution, metabolism, and excretion, and equilibrium is reestablished between bound and unbound drug, thus maintaining a constant serum level.
- Second, many drugs have a large therapeutic index; thus, even a doubling of the serum level will not result in clinically observable effect.
- Third, the time between the pharmacokinetic interaction of displacement and the pharmacodynamic response can be too great for the interaction to be relevant.
- For example, warfarin is highly protein bound and can be displaced by many drugs such as phenytoin, phenylbutazone, and disulfiram. This displacement occurs quickly with rapid changes in serum warfarin levels.
- However, the anticoagulant action of warfarin takes several days to change because of the long half-lives of some of the vitamin K–dependent clotting factors that it inhibits.
- Before a new steady state can be reached for these clotting factors, warfarin equilibrium is reestablished and no effect from protein displacement is observed.
- Note, however, that these drugs do have clinically significant interactions with warfarin because of changes in warfarin metabolism.

✓ **Altered Drug Transport**

- The degree to which transporters control the distribution of drugs has become better appreciated with advances in this field, which can now explain the pharmacology of many compounds.
- For example, Pgp in the endothelial cells of brain capillaries is oriented to pump drug out of the cell and into the blood, thus limiting distribution of many drugs, chemicals, and toxins.
- Fexofenadine is a nonsedating antihistamine by virtue of the fact that it is a Pgp substrate and does not reach the central nervous system (CNS).

- First-generation antihistamines are not Pgp substrates, resulting in CNS exposure and sedation.
- Although clinically significant drug interactions such as these are few, they can occur.
- Loperamide is an opiate antidiarrheal that has minimal CNS effects because Pgp prevents its distribution into the CNS.
- When it is combined with the Pgp inhibitor quinidine, however, CNS loperamide concentrations can reach levels that produce respiratory depression.

- **HEPATIC METABOLISM**
  - ✓ **Cytochrome P-450**
    - Pharmacokinetic interactions that involve changes in metabolism account for most therapeutically important drug interactions.
    - As has already been reviewed, some metabolism occurs in the intestine.
    - Other metabolic sites include the kidneys, the lungs, and the blood itself, but by and large, most metabolic activity occurs in the endoplasmic reticulum of hepatocytes in the liver.
    - The main enzymes responsible for drug metabolism are the CYP450 enzymes; of these, CYP1A2, 2C9, 2C19, 2D6, 2E1, and 3A4 are most often involved in drug metabolism.
    - Metabolic drug interactions occur when enzymes responsible for metabolism are inhibited or induced by another drug.
    - The most common and important mechanism for drug interactions is inhibition, because of its potential to elevate drug levels, increase drug response, and cause toxicity.
    - Drug-induced inhibition occurs quickly, usually within hours after introduction of the inhibitor.
    - However, the full effect is concentration dependent and is determined by the half-life of the inhibitor.
    - For example, fluoxetine, an inhibitor of CYP2D6, has a half-life of 4 to 6 days after long-term administration. Although inhibition of 2D6 will begin shortly after fluoxetine therapy starts, its full impact on 2D6, and on any drugs metabolized by this enzyme, will not be realized for approximately 1 month.
    - On the other hand, quinidine, also a 2D6 inhibitor, has a half-life of 6 to 8 hours. Subsequently, the full effect of its interaction with a 2D6 substrate will be evident within 2 days.
    - In the same way, the offset of an inhibition interaction will depend on the half-life of the inhibitor.

- Continuing with the fluoxetine example, it has been observed that inhibition interactions are possible for up to 4 to 6 weeks after the last dose is taken, which is the length of time it will take before fluoxetine levels are negligible.
- Inhibition of drug metabolism occurs when a drug (the inhibitor) slows down the metabolic activity of the enzyme responsible for metabolism of a substrate drug.
- Inhibition can be reversible or irreversible, with the former being the more common process.
- **Reversible inhibition** occurs by one of three mechanisms: **competitive inhibition** (competition between the inhibitor and the substrate for the active site on the enzyme; this prevents substrate binding), **noncompetitive inhibition** (binding of the inhibitor with no effect on the binding of the substrate to the active site), or **uncompetitive inhibition** (binding of the inhibitor to the enzyme–substrate complex; this renders it ineffective).
- **Irreversible inhibition** occurs when the perpetrator drug forms a reactive intermediate with the enzyme that permanently inactivates the enzyme.
- Drug interactions that result from irreversible inhibition tend to be more profound than those caused by reversible inhibition.
- Drugs known to cause irreversible inhibition interactions include erythromycin, diltiazem, paroxetine, and spironolactone.
- Following irreversible inhibition, the return of normal enzyme activity is dependent on both the half-life of the perpetrator drug and the synthesis of new enzyme molecules.
- The opposite of inhibition is induction, whereby the inducing drug boosts the synthesis of the enzyme(s) responsible for metabolism of the substrate drug.
- Mechanistically, the inducer usually does not interact directly with the enzyme itself.
- Instead, inducers bind to specific sites on the genes that regulate enzyme synthesis, called *nuclear receptors*; these stimulate gene transcription and enzyme production.
- Similar to inhibition, enzyme induction is dose dependent.
- Thus, the onset of an induction interaction is gradual because it depends on accumulation of the inducer, as well as on new enzyme synthesis.
- Consequently, the full effect of the inducing drug may not be seen for several weeks after the inducer is introduced, in contrast to the

impact of inhibition interactions, which may be fully evident within days.

- The offset of induction interactions is also gradual because it depends upon the elimination of both the inducer and the metabolizing enzyme(s) until a return to the baseline rate of enzyme production is achieved.
- Less common mechanisms of enzyme induction include stabilization of the enzyme–substrate complex, processing of messenger RNA (mRNA), stabilization of mRNA, and increased translation.
- Induction interactions tend to be less prominent than inhibition interactions because elevated drug levels, and therefore drug toxicity, rarely occur.
- However, therapeutic failure from lowered plasma levels following enzyme induction is well documented and can be significant.
- For example, rifampin, a potent inducer of CYP3A4, can lower levels of the CYP3A4 and Pgp substrate cyclosporine, leading to acute organ graft rejection. Rifampin affects hepatic and intestinal 3A4, as well as intestinal Pgp. Consequently, rifampin interacts with cyclosporine by all three mechanisms—increased intestinal and hepatic metabolism and increased efflux via Pgp.
- Amplified drug metabolism can also lead to increased production of active metabolites or toxic intermediates.
- For example, isoniazid is an inducer of CYP2E1 that causes increased production of a hepatotoxic metabolite of acetaminophen.

✓ **First-Pass Effect**

- The first-pass effect describes the metabolism of a drug before it reaches the systemic circulation and is a key determinant of bioavailability.
- It can be seen that the intestine and liver work coordinately to affect drug metabolism.
- Subsequently, the extent and rate of intestinal metabolism affect the extent and rate of hepatic metabolism.
- Notably, although these two organs work together, their metabolic capabilities are independently controlled and regulated.
- Drug interactions that affect the cytochrome P-450 system and/or intestinal transporters like Pgp can alter the oral bioavailability of the target drug, either by increasing its first-pass metabolism (enzyme induction causing low bioavailability) or by lowering its first-pass metabolism (enzyme inhibition causing increased bioavailability).

- **Non–Cytochrome P-450 Metabolism—Phase I Reactions**
  - ✓ Many other phase I enzymes are responsible for drug metabolism.

MAJOR ENZYMES INVOLVED IN DRUG BIOTRANSFORMATION		
Clearance Mechanism	**Phase of Metabolism**	**Enzymes/Proteins Involved**
Oxidative metabolism	Phase I	CYP, MAO, FMO, Mo-CO, aldehyde oxidase, xanthine oxidase, peroxidases
Hydrolytic metabolism	Phase I	Esterases, amidases, epoxide hydrolases
Conjugative metabolism	Phase II	UGT, ST, MT, NAT, GST
CYP, cytochrome P450 enzymes; MAO, monoamine oxidases; FMO, flavin-containing monooxygenases; Mo-CO, molybdenum-containing oxidases; UGT, uridine diphosphate–glucuronyltransferases; ST, sulfotransferases; MT, methyltransferase; NAT, N-acetyltransferase; GST, glutathione-S-transferase.		

- **Non–Cytochrome P-450 Metabolism—Phase II Reactions**
  - ✓ Phase II reactions are conjugations whereby a transferase attaches a polar molecule such as glucuronic acid, sulfate, or a methyl group to a drug to enhance its elimination.
  - ✓ Generally speaking, the enzymes involved in phase II reactions, similar to those catalyzing non–cytochrome P-450 metabolism, are not a major source of drug interactions for many of the same reasons.
  - ✓ As has previously been stated, most phase II reactions involve a product of phase I metabolism.
  - ✓ Compared with phase I reactions, fewer drugs undergo a phase II reaction as the initial or primary metabolic route.
  - ✓ There are some notable exceptions.
  - ✓ For example, morphine, zidovudine, epinephrine, norepinephrine, hydralazine, isoniazid, and azathioprine are metabolized principally by phase II reactions.
  - ✓ Of the phase II processes, glucuronidation via UDP-glucuronyltransferase (UDPGT) is the most common and most studied.
  - ✓ Analogous to the cytochrome P-450 enzymes, the UGTs are a superfamily of enzymes.
  - ✓ More than 33 families of UDPGTs have been identified, and these are subdivided into families and subfamilies on the basis of amino acid sequence homology, similar to the cytochrome P-450 system.
  - ✓ Nomenclature similar to that of the P-450 system has been adopted for the UGTs.

- ✓ Thus, just as CYP3A4 and CYP2D6 represent different enzymes in the same cytochrome family, UGT1A1 and UGT2B7 are different enzymes in the UGT family.
- ✓ Among the UGTs, the UGT1 and UGT2 families are the most important in human drug metabolism.
- ✓ Similar to the CYP enzymes, some of the UGT enzymes, most notably, UGT1A1, 1A6, 2B4, 2B7, and 2B15, display polymorphism.
- ✓ Many of the drugs that induce the CYP enzymes coinduce the UGT enzymes such as phenobarbital, phenytoin, and rifampin.
- ✓ Specific inhibitors of the UGT system have not been identified; however, any substrate for UDPGT has the potential for competitive inhibition of another substrate metabolized by the same enzyme.
- ✓ Many UGT drug interactions have been identified from in vitro and in vivo studies but have not been clinically validated. There are some exceptions, however.
- ✓ For example, the combination of lamotrigine and valproic acid has led to CNS toxicity in four cases.
- ✓ Glucuronidation of lamotrigine was felt to be competitively inhibited by valproic acid, leading to elevated lamotrigine levels and neurotoxicity.
- ✓ A similar explanation has been offered for a case of coma following the combination of valproic acid and lorazepam and for a case of anemia following valproic acid and zidovudine.
- ✓ Induction reactions with UGTs have also been reported, although again such reactions with clinical relevance are few.[75,76,77] As genetic and molecular research techniques improve, drug interactions involving all phase II enzymes will likely grow in clinical importance as well.

- **ELIMINATION**
  - ✓ With the exception of inhaled anesthetics, most drugs or drug metabolites are eliminated from the body via the urine or the bile.
  - ✓ Other means of elimination are possible, for example, via sweat, saliva, or in the breast milk of nursing mothers. By and large, however, these are insignificant compared with the biliary and renal routes.
  - ✓ **Renal Elimination**
    - o To review, blood enters the kidney via the renal artery, traveling first to the glomeruli. Pores in the glomerular membrane allow water, salts, and some drugs into the lumen of the tubules, while larger molecules and proteins such as albumin are retained.

- Blood flow then passes to the remaining portions of the kidney, where transport proteins can actively secrete endogenous substances, as well as drugs, into the tubular lumen.
- Tubular cells in the lumen also have the capacity for active and passive reabsorption of these substances.

✓ **Passive Diffusion**

- Drugs in the kidney tubule may be reabsorbed back into the plasma by passive diffusion.
- This process is optimal when the drug is in its nonionized form, that is, in its most lipid-soluble state.
- Thus, the pKa of the drug and the pH of the urine influence the extent of passive reabsorption that a drug undergoes.
- Weakly acidic drugs exposed to alkaline urine are in their most ionized state, have minimal reabsorption, and are excreted in the urine.
- The same holds true for weakly basic drugs in acidic urine.
- On the other hand, reabsorption is enhanced for acidic drugs in acidic urine and alkaline drugs in alkaline urine.
- Drugs that alter urinary pH may therefore influence renal elimination.
- For example, magnesium-containing antacids may elevate urine pH sufficiently to increase reabsorption of the basic antiarrhythmic drug quinidine, causing potentially toxic serum levels.
- Similarly, aspirin effectiveness may be decreased by concurrent antacid use owing to enhanced elimination.
- Despite these examples, drug interactions that result from changes in urinary pH are generally not clinically important.
- This is because most drugs undergo some metabolism before being eliminated in the urine.
- Also, many drugs that are excreted unchanged and may be affected by drug-induced changes in urine pH have a wide therapeutic index, such that an elevated plasma level has a negligible clinical impact.

✓ **Active Transport**

- The renal proximal tubule is the primary site of active transport for a wide variety of substrates, including organic anions/cations, peptides, nucleosides, and drugs.
- Many drug transporters are responsible for both the active secretion and the reabsorption of drugs in the kidney.
- Drug interactions can arise from many of the mechanisms already described, including competitive inhibition between two or more drugs for the same transport protein, and induction or inhibition of transporter production or function.

- Inhibition of renal P-glycoprotein has been well researched, particularly with the Pgp substrate digoxin.
- Located at the brush border membrane of the nephron, Pgp drives hydrophobic substances, such as digoxin, into the renal proximal tubule, aiding in their elimination.
- Blocking of the action of renal Pgp by known Pgp inhibitors such as clarithromycin, quinidine, itraconazole, and ritonavir decreases digoxin excretion into the proximal tubule and elevates plasma digoxin levels.
- Some drug interactions can now be explained by the impact of the perpetrator drug on Pgp at multiple locations.
- Quinidine, for example, blocks intestinal Pgp, thus increasing oral digoxin bioavailability; it also inhibits renal Pgp, thus blocking renal elimination of digoxin and causing elevated plasma levels.
- One might anticipate that induction of renal Pgp may lead to enhanced renal elimination of Pgp substrates, although this has not yet been well documented.
- Organic anion and cation transporters in the kidney are involved in several notable drug interactions.
- The organic anion transport (OAT) inhibitor probenecid, for example, blocks the tubular secretion of the OAT substrates ciprofloxacin, many penicillins and cephalosporins, zalcitabine, acyclovir, ganciclovir, methotrexate, and angiotensin-converting enzyme (ACE) inhibitors, causing increased plasma levels and drug exposure.
- This interaction may be used to therapeutic benefit, as with coadministration of probenecid and penicillin to increase plasma penicillin levels, or probenecid given with cidofovir to minimize cidofovir nephrotoxicity.
- However, significant toxicity may also occur from such interactions. Competitive inhibition between methotrexate and a nonsteroidal anti-inflammatory drug (NSAID) or a penicillin antibiotic for an OAT can produce elevated methotrexate levels and bone marrow suppression in patients receiving high-dose methotrexate therapy.
- Fewer drug interactions have been reported that involve organic cation transporter (OCT) proteins.
- However, cimetidine and triamterene are potent inhibitors of OCT that block the secretion of procainamide and its active metabolite N-acetylprocainamide (NAPA), potentially causing cardiac toxicity due to elevated procainamide and NAPA levels.

- Despite these noteworthy examples, clinically important interactions involving renal transport proteins remain relatively few.
- However, information on the specific substrates, inducers, and inhibitors of the numerous renal transport proteins thus far discovered is still emerging, and their role in drug interactions is yet to be fully appreciated.

✓ **Biliary Elimination**

- Hepatobiliary elimination is the primary means of elimination for many drugs and drug metabolites.
- Drugs in the blood enter hepatocytes by crossing the sinusoidal membrane.
- Within the hepatocyte, a drug may be transported to a metabolic site (e.g., the cytochrome P-450 system in the endoplasmic reticulum) or carried to the biliary canalicular membrane of the hepatocyte.
- Finally, a drug, its metabolite(s), or both cross the canalicular membrane into the bile for excretion in the feces or possibly for enterohepatic recirculation.
- Each stage of this three-step process can occur by passive diffusion or active transport.
- Several of the transport proteins involved in each stage and their drug substrates have been identified.
- The organic anion–transporting polypeptide (OATP) family plays a significant role in transport of substances across the sinusoidal membrane of the hepatocyte.
- Although the name suggests that substrates are limited to organic anions, in fact, this family of proteins has broad substrate specificity that includes both neutral and basic compounds.
- Drug substrates include digoxin, pravastatin, fexofenadine, and rocuronium, as well as many drug metabolites such as N-methylquinidine and estradiol glucuronide.
- Among the several proteins that make up this family, OATP-C and OATP-8 are the most important and are linked to significant drug interactions.
- For example, cyclosporine, a known inhibitor of OATP-C, has been shown to increase rosuvastatin exposure by more than sevenfold in transplant recipients compared with historical controls not receiving cyclosporine.
- Using an in vitro model, the same investigators established that rosuvastatin is an OATP-C substrate and proposed that cyclosporine inhibited the OATP-C–mediated transport of rosuvastatin across hepatocytes, leading to elevated drug levels.

- This is important clinically in that myopathy and rhabdomyolysis from statin drugs are in part concentration dependent.
- The interaction between cyclosporine and statin drugs is well documented and has previously been explained by cyclosporine-mediated inhibition of statin metabolism via CYP3A4 because many of these compounds are 3A4 substrates.
- Rosuvastatin, though, undergoes very little metabolism through the CYP2C9 pathway and is not significantly affected by CYP inhibitors such as cyclosporine, thus supporting that it is inhibition of OATP-C that is the cause of the interaction.
- Because other statins such as atorvastatin and cerivastatin are also OATP-C substrates, the interaction between these drugs and cyclosporine may involve inhibition of CYP3A4 metabolism, as well as OATP-C uptake.
- The combination of gemfibrozil and a statin is also known to increase the risks of myopathy and rhabdomyolysis.
- A recent study found that gemfibrozil inhibited OATP-C–mediated uptake of rosuvastatin in vitro and caused a twofold elevation in plasma rosuvastatin exposure in healthy volunteers, suggesting a possible role in gemfibrozil–statin interactions.
- Although the antitubercular drugs rifampin and rifamycin SV are best known as enzyme inducers, they are also both inhibitors of human OATP-C and OATP-8 in vitro, and their role in drug interactions via this mechanism is being studied.
- Members of the ABC family of transporters, including P-glycoprotein, canalicular multispecific organic anion transporter (cMOAT), MRP1, and sister-Pgp, are the primary proteins involved in movement of substances across the canalicular membrane of the hepatocyte and into the bile.
- Canalicular Pgp substrates include cyclosporine, paclitaxel, vincristine, vinblastine, digoxin, loperamide, and doxorubicin.

PHARMACODYNAMICS

- Although most significant drug interactions involve a pharmacokinetic mechanism, numerous pharmacodynamic interactions are clinically important as well.
- Pharmacodynamic interactions can be divided into one of two mechanisms: **synergistic** and **antagonistic**.
- **SYNERGISTIC INTERACTIONS**
  - ✓ Two drugs with similar pharmacologic profiles when taken together can produce a response greater than that of either drug alone.

- ✓ This can occur independent of changes to any pharmacokinetic parameter.
- ✓ This is an example of a synergistic (also called *additive*) pharmacodynamic interaction.
- ✓ For example, a patient taking amitriptyline for depression who is prescribed benztropine for Parkinson's disease may experience additive anticholinergic effects.
- ✓ These can manifest as severe constipation, dry mouth, worsening vision, or psychosis.
- ✓ The synergistic mechanism may not always be clear, however. For instance, the combination of an erectile dysfunction drug such as sildenafil, vardenafil, or tadalafil and a nitrate such as isosorbide mononitrate causes profound hypotension.
- ✓ The former drugs reverse erectile dysfunction by inhibiting phosphodiesterase type 5 (PDE5), which is responsible for the metabolism of cyclic guanosine monophosphate (cGMP).
- ✓ Although PDE5 is primarily located in the corpus cavernosum of the penis, it is also present in the systemic vasculature, where elevated cGMP causes vasodilation. Nitric oxide donors such as isosorbide mononitrate, nitroglycerin, or isosorbide dinitrate exert their vasodilatory effects by ultimately increasing cGMP levels.
- ✓ Because these two drug classes have additive effects on cGMP and blood pressure, the combination of a PDE5 inhibitor and any nitrate is contraindicated.

- **Antagonistic Interactions**
  - As the name implies, the end result of an antagonistic pharmacodynamic interaction is a degradation or blunting of the response to one or both interacting drugs.
  - For example, corticosteroids can cause hyperglycemia, worsening blood glucose control for diabetic patients, which may require changes in insulin dosing.
  - Similarly, the antidepressant mirtazapine has been reported to block α-receptors, causing loss of hypertensive control in patients taking clonidine.
  - Frequently, a pharmacodynamic interaction may be difficult to detect and may be interpreted as loss of drug effect or worsening of disease.
  - Take the case of a patient with Alzheimer dementia who is receiving treatment with the cholinesterase inhibitor donepezil and is prescribed the anticholinergic drug tolterodine for urinary incontinence.
  - Without a complete understanding of the pharmacodynamic principles, the patient's deteriorating mental state could simply be attributed to worsening Alzheimer's disease, instead of to the loss of cholinergic effect of donepezil caused by tolterodine, especially because this is a progressive illness.

- It is therefore essential that clinicians be vigilant for pharmacodynamic interactions and fully evaluates any change in patient symptoms or disease state after drug therapy is added or deleted.

Food–Drug Interactions

- Food–drug interactions are extensive and in some ways more complex than drug–drug interactions.
- The presence or absence of food, the composition of the meal and its size, the formulation of the drug, and even the age of the patient all factor into food–drug interactions.
- Moreover, not only must the impact of food and diet on a drug be considered, but the effect of a drug on diet and nutrition must be evaluated as well.
- For example, any drug that induces nausea or vomiting can influence oral intake and the nutritional state of the patient.
- Antineoplastic drugs are among the most notorious emetogenic agents, and many also severely affect the gastric mucosa, which alters the absorptive processes of foods and nutrients.
- Drugs that affect taste, such as metronidazole, captopril, or penicillamine, may cause decreased appetite, decreased oral intake, and poor nutrition.
- Vitamins and minerals that are dependent upon an acidic environment for absorption can be affected by proton pump inhibitors, H_2-receptor blockers, and antacids, leading to deficiencies.
- Hypertriglyceridemia from propofol, parenteral nutrition, cyclosporine, or tacrolimus is well known.
- Last, numerous drugs cause electrolyte losses, including diuretics, many antineoplastics, laxatives, and antimicrobials.
- Clearly, the impact of drugs on nutrition should not be overlooked.
- The impact of food on drugs may be pharmacokinetic or pharmacodynamic in nature, with the former being the most common.
- As with drug–drug interactions, the clinical importance of a food–drug interaction is determined by the magnitude of the interaction and the therapeutic index of the drug.
- The most important pharmacokinetic food–drug interactions are those that alter the absorption of a drug.
- This may occur through one of the mechanisms previously described for drug–drug interactions, namely, chelation, adsorption, changes in gastric pH, altered GI motility, altered gut metabolism, or altered transport across the gastric mucosa.
- How food influences drug absorption is not easily predicted.
- The presence of food in the GI tract can increase, decrease, or have no effect on the absorption of a drug.

- Food stimulates gastric acid secretion, thus reducing gastric pH, increases gastric emptying, and slows small intestine transit time, any of which may affect drug solubility and/or absorption.
- The protease inhibitor saquinavir, for instance, has negligible absorption when taken on an empty stomach, which can lead to therapeutic failure.
- Taken with food, however, its bioavailability increases by 600% to 1,800%.
- Furthermore, a heavy meal increases bioavailability to a greater extent than does a light meal.
- Meal composition can change drug bioavailability.
- A high-fat meal significantly reduces the absorption of the protease inhibitor indinavir compared with the fasting state, but a low-fat meal has no major effect on its absorption.
- Drug dosage form can also be important in determining the effect of food. Azithromycin capsules should be taken 1 hour before or 2 hours after a meal because food significantly lowers its bioavailability; azithromycin tablets and suspension may be taken without regard to a meal.
- Given the unpredictability of the effects of food on medicines, it is essential that clinicians avoid generalizations and instead review prescribing information and pertinent pharmacokinetic literature, especially for new drugs and dosage forms.

PREVENTAION OF DRUG INTERACTIONS

- Evaluate drug interaction risk on a patient-specific basis
- Use computerized drug interaction programs as a screening tool only
- Use additional sources of drug interaction information to supplement the program
- Develop and regularly update a list of “red flag” drugs made up of highly potent inducers and inhibitors, as well as narrow therapeutic index drugs
- Ask patients about all medicines—traditional, over-the-counter, and alternative—before you start any new medicines. Questioning specifically about alternative medicines is especially important because many patients are reluctant to freely offer such information. Many patients are also under the misconception that alternative medicines are “weak” and will not interact with traditional drugs; that alternative medicines are free of adverse effects because they are “natural,” or “they must be safe or they would be regulated”; or that alternative medicines are not medicines at all. Education is critical to these patients
- Offer non interacting alternatives to victim or perpetrator drugs whenever possible
- If non interacting alternatives are unavailable, use low-risk perpetrator drugs and/or find a victim drug with parallel metabolic pathways

- If interacting drugs must be used concomitantly, take steps to mitigate the interaction, such as staggering administration times or changing dosage forms
- Monitor the patient if it appears that the chance of interaction is high and the outcome is likely to be clinically meaningful
- Look at any sudden change in patient status as a potential result of a drug interaction, and investigate. Remember that starting *or* stopping a perpetrator drug can affect a victim drug and patient status
- Educate other clinicians and patients about the risks of drug interactions and what signs and symptoms to watch out for

PRESCRIPTION MONITORING DOCUMENTATION AND MINIZATION OF DRUG INTERACTIONS:

PRESCRIPTION MONITORING:

- Assessing possible drug interaction in case of multiple therapies (Prescription review)
- Preventing and/ or managing drug interactions will be more likely to occur when the pharmacist takes time and utilizes and adequate patient data base that include the
  - ✓ Patient's name
  - ✓ Gender
  - ✓ Age
  - ✓ Vital signs
  - ✓ Medical diagnosis
  - ✓ Drug allergies
  - ✓ Relevant laboratory tests
  - ✓ Complete listing of medication being taken routinely or taken on an as-needed basis.
- If the pharmacist lacks essential patient data, he/she may obtain it from the patient. In addition, with the patient's permission, the pharmacist may call the physician to get essential monitoring information, such as results of recent lab tests or a complete list of medical diagnosis.
- Complete analysis of patient prescription will help to justify the medication and dose of the individuals prevent the drug interactions.

CLINICAL MANAGEMENT OF DRUG INTERACTIONS

- Clinical management of drug-drug interactions should include prospective and concurrent patient, disease- and drug –monitoring measures that are sensitive enough to alert the pharmacist or healthcare provider to monitor specific patient, disease-or drug therapy parameters and whenever possible, correlate these finding with clinical laboratory tests. Follow-up monitoring of a patient's therapy and making appropriate adjustments in the drug regimen can circumvent potentially significant drug interactions.
- Patients at high risk for drug interactions who also take drugs with narrow therapeutics index should be monitored more closely for drug interactions, especially when a new drug is added or discontinued.

- Depending on the drugs in question, likely drug interactions will generally occur within a few days following a change in drug regimen.
- If two drugs have been identified as having high potential to interact and cause harm, the pharmacist can contact the patient's physician to obtain an order for another medication that will not cause the troublesome interactions.
- In some instance a patient's diet or lack of adherence to a specified diet may be part of the problem. These situations may require the assistance of a dietitian to resolve.

MINIMIZATION OF DRUG INTERACTION:

- Clinicians should know all of their patient's current drugs, including drugs prescribed by other clinicians and all OTC drugs, herbal products and nutritional supplements.
- Asking patients relevant questions about diet and alcohol consumption is recommended.
- The fewest drugs in the lowest doses for the shortest possible time should be prescribed.
- The effects, desired and undesired, of all drugs taken should be determined because these effects usually include the spectrum of drug interactions.
- If possible, drugs with a wide safety margin should be used so that any unforeseen interactions do not cause toxicity.
- Patient should be observed and monitored for adverse effects, particulary after a change in treatment; some interactions may take > 1 week to appear.
- Drug interactions should be considered as a possible cause of any unexpected problems. When unexpected clinical responses occur, prescribers should determine serum concentrations of selected drugs being taken consult the expert in drug interactions and adjust the dosage until the desired effect is produced.
- If dosage adjustment is ineffective, the drug should be replaced by one that does not interact with other drugs being taken.
- Avoiding Misuse of Medications
- Avoiding Overuse of Medications
  - ✓ Polypharmacy
  - ✓ Overdosing
- Avoiding Underuse of Medications
  - ✓ Under prescribing
  - ✓ Non-adherence

DOCUMENTATION AND DETECTION OF DRUG INTERACTIONS

- Source of drug interaction information
- Literature
- In-vitro-and animal data
- Case reports
- Clinical study reports
- Reviews

- Monographs
- Book sources
- Drug tables
- Drug charts
- Drug data sheets
- Drug interactions websites