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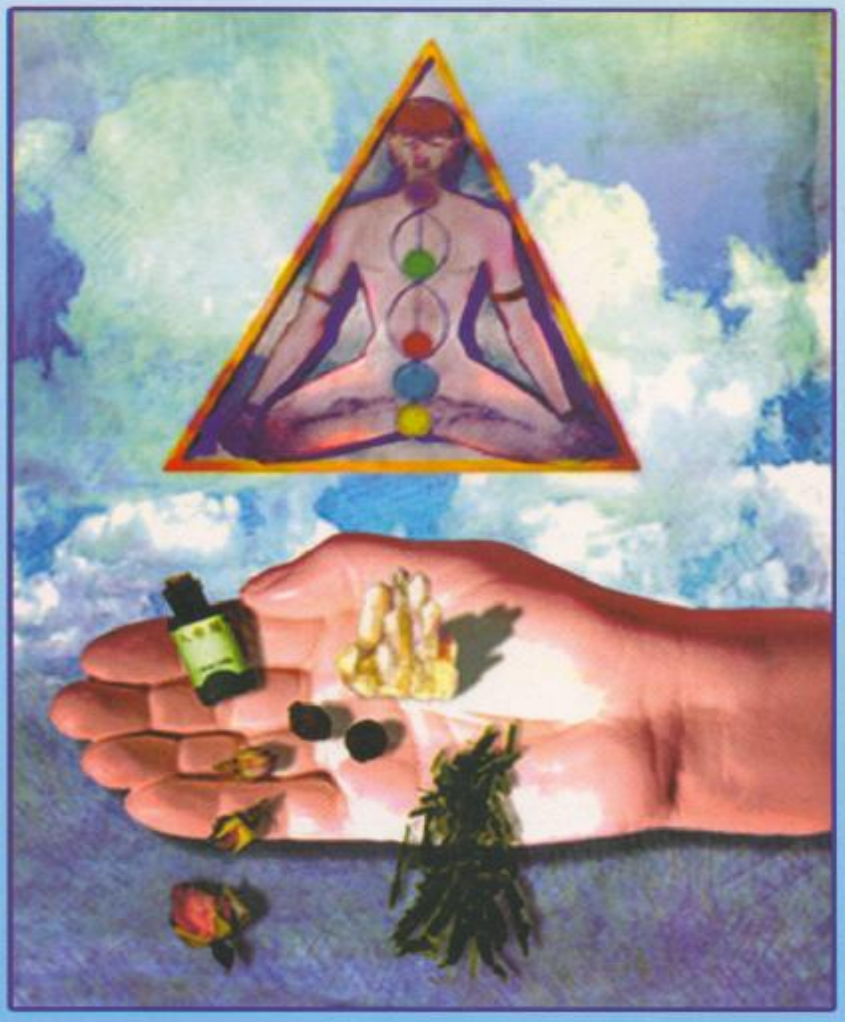
Drug-Drug
Herb-drug & Food-drug
Interactions



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Drug – Drug Interactions

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DRUG INTERACTIONS

The administration of one drug (A) can alter the action of another (B) by one of two general mechanisms:

• Modification of the pharmacological effect of B without altering its concentration in the tissue fluid (pharmacodynamic interaction)

• Alteration of the concentration of B that reaches its site of action (pharmacokinetic interaction).

1) For such interactions to be important clinically it is necessary that the therapeutic range of drug B is narrow (i.e. that a small reduction in effect will lead to loss of efficacy and/or a small increase in effect will lead to toxicity).

2) For pharmacokinetic interactions to be clinically important it is also necessary that the dose-response curve of drug B is steep (so that a small change in plasma concentration leads to a substantial change in effect).

3) For many drugs these conditions are not met: even quite large changes in plasma concentrations of relatively non-toxic drugs like penicillin are unlikely to give rise to clinical problems because there is usually a comfortable safety margin between plasma concentrations produced by usual doses and those resulting in either loss of efficacy or toxicity.

4) Several drugs do have steep dose-response relationships and a narrow therapeutic margin and drug interactions can cause major problems, for example with antithrombotic, antidysrhythmic and anti-epileptic drugs, lithium and several antineoplastic and immunosuppressant drugs.

N.B. A third category of pharmaceutical interactions should be mentioned, in which drugs interact in vitro so that one or both are inactivated. No pharmacological principles are involved, just chemistry. An example is the formation of a complex between thiopentone and suxamethonium, which must not be mixed in the same syringe. Heparin is highly charged and interacts in this way with many basic drugs; it is sometimes used to keep intravenous lines or cannulae open, and can inactivate basic drugs' if they are injected without first clearing the line with saline.

Pharmacodynamic interaction

Pharmacodynamic interaction can occur in many different ways. There are many mechanisms, and some examples of practical importance are probably more useful than attempts at classification. Consider the following:

• β-adrenoceptor antagonists diminish the effectiveness of β-receptor agonists, such as salbutamol or terbutaline.

• Many diuretics lower plasma potassium concentration, and thereby enhance some actions of digoxin and predispose to glycoside toxicity.

• Monoamine oxidase inhibitors increase the amount of norepinephrine stored in noradrenergic nerve terminals and thereby interact dangerously with drugs, such as ephedrine or tyramine that work by releasing stored norepinephrine. This can also occur with tyramine-rich foods—particularly fermented cheeses such as Camembert.

• Warfarin competes with vitamin K, preventing hepatic synthesis of various coagulation factors. If vitamin K production in the intestine is inhibited (e.g. by antibiotics), the anticoagulant action of warfarin is increased. Drugs that cause bleeding by distinct mechanisms (e.g. aspirin, which inhibits platelet thromboxane A_2 biosynthesis and can damage the stomach) increase the risk of bleeding caused by warfarin.

• Sulphonamides prevent the synthesis of folic acid by bacteria and other microorganisms; trimethoprim inhibits its reduction to tetrahydrofolate. Given together the drugs have a synergistic action of value in treating Pneumocystis carinii.

• Non-steroidal anti-inflammatory drugs (NSAIDs), such as ibuprofen or indomethacin, inhibit biosynthesis of prostaglandins, including renal vasodilator/natriuretic prostaglandins (PGE_2, PGI_2). If administered to patients receiving treatment for hypertension, they cause a variable but sometimes marked increase in blood pressure, and if given to patients being treated with diuretics for chronic heart failure can cause salt and water retention and hence cardiac decompensation.

N. B. The interaction with diuretics may involve a pharmacokinetic interaction in addition to the pharmacodynamic effect described here, because NSAIDs can compete with weak acids, including diuretics, for renal tubular secretion (see below).

• H_1-receptor antagonists, such as mepyramine, commonly cause drowsiness as an unwanted effect. This is more troublesome if such drugs are taken with alcohol, and may lead to accidents at work or on the road.

Pharmacokinetic interaction

All of the four major processes that determine the pharmacokinetic behaviour of a drug—absorption, distribution, metabolism and excretion—can be affected by co-administration of other drugs. Some of the important mechanisms are given here, with examples.

I) Absorption

- Gastrointestinal absorption is slowed by drugs that inhibit gastric emptying, such as atropine or opiates, or accelerated by drugs (e.g. metoclopramide) which hasten gastric emptying.

- Alternatively, drug A may interact with drug B in the gut in such a way as to inhibit absorption of B, e.g.

A) Calcium (and also iron) forms an insoluble complex with tetracycline and retards its absorption

B) Cholestyramine, a bile acid binding resin used to treat hypercholesterolaemia, binds several drugs (e.g. warfarin, digoxin) preventing their absorption if administered simultaneously.

C) Addition of epinephrine to local anesthetic injections: the resulting vasoconstriction slows the absorption of the anaesthetic, thus prolonging its local effect.

II) Distribution

- § Displacement of a drug from binding sites in plasma or tissues transiently increases the concentration of free (unbound) drug, but this is followed by increased elimination so a new steady state results, in which total drug concentration in plasma is reduced but the free drug concentration is similar to that before introduction of the second 'displacing' drug.

- § There are several direct consequences of potential clinical importance:

1) Toxicity from the transient increase in concentration of free drug, before the new steady state is reached.

2) If dose is being adjusted according to measurements of total plasma concentration, it must be appreciated that the target therapeutic concentration range will be altered by coadministration of a displacing drug.

3) When the displacing drug additionally reduces elimination of the first, so that not only is the free concentration increased acutely, but also chronically at the new steady state, severe toxicity may ensue.

4) Though many drugs have appreciable affinity for plasma albumin and therefore might potentially be expected to interact in these ways, there are rather few instances of clinically important interactions of this type.

5) Protein-bound drugs that are given in large enough dosage to act as 'displacing agents' include aspirin and various sulphonamides, as well as chloral hydrate whose metabolite, trichloracetic acid, binds very strongly to plasma albumin.

6) Displacement of bilirubin from albumin by such drugs in jaundiced premature neonates could have clinically disastrous consequences: bilirubin metabolism is undeveloped in the premature liver, and unbound bilirubin can cross the blood-brain barrier (which is also incompletely developed) and cause kernicterus (staining of the basal ganglia by bilirubin). This causes a distressing and permanent disturbance of movement known as

choreoathetosis, characterised by involuntary writhing and twisting movements in the child.

7) Phenytoin dose is adjusted according to measurement of its concentration in plasma, and such measurements do not routinely distinguish bound from free phenytoin (that is, they reflect the total concentration of drug). Introduction of a displacing drug in an epileptic patient stabilised on phenytoin reduces the total plasma phenytoin concentration owing to increased elimination of free drug, but no loss of efficacy because the concentration of unbound (active) phenytoin at the new steady state is unaltered. If it is not appreciated that the therapeutic range of plasma concentrations has been reduced in this way, an increased dose may be prescribed resulting in toxicity.

8) There are several instances where drugs that alter protein binding additionally reduce elimination of the displaced drug, causing clinically important interactions:
A) Phenylbutazone displaces warfarin from binding sites on albumin and more importantly selectively inhibits metabolism of the pharmacologically active S isomer (see below), prolonging prothrombin time and resulting in increased bleeding.

B) Salicylates displace methotrexate from binding sites on albumin and reduce its secretion into the nephron by competition with the anion secretory carrier.

C) Quinidine and several other antidysrhythmic drugs including verapamil and amiodarone displace digoxin from tissue-binding sites while simultaneously reducing its renal excretion, and can consequently cause severe dysrhythmias due to digoxin toxicity.

III) Metabolism

Some examples of drugs that inhibit or induce drug metabolism are shown in the following table:

Examples of drugs that induce or inhibit drug-metabolising enzymes	
Enzyme induction	
Drugs modifying enzyme action	***Drugs whose metabolism is affected***
Phenobarbitone and other barbiturates Rifampin Griseofulvin Phenytoin Ethanol Carbamazepine	Warfarin Oral contraceptives Corticosteroids Cyclosporin (as well as drugs listed in left-hand column)
Enzyme inhibition	
Drugs modifying enzyme action	***Drugs whose metabolism is affected***
Disulfiram	Warfarin
Allopurinol	Mercaptopurine, azathioprine
Ecothiopate and other anticholinesterases	Suxamethonium, procaine
Chloramphenicol	Phenytoin
Corticosteroids	Various drugs, e.g. tricyclic antidepressants, cyclophosphamide
Cimetidine	Many drugs, e.g. amiodarone, phenytoin, pethidine
MAO inhibitors	Pethidine
Erythromycin	Cyclosporin, theophylline
Ciprofloxacin	Theophylline

1) Enzyme induction

- Over 200 drugs cause enzyme induction and thereby decrease the pharmacological activity of a range of other drugs.

- Induction (stimulation) of cytochrome isozymes in the liver and small intestine can be caused by drugs such as barbiturates, carbamazepine, glutethimide, phenytoin, primidone, rifampin, and troglitazone.

- Since the inducing agent is normally itself a substrate for the induced enzymes, the process can result in slowly developing tolerance.

- § Although this pharmacokinetic kind of tolerance is generally less important clinically than tolerance that results from pharmacodynamic adaptations (e.g. to opioid analgesics), and the lethal dose of inducing drugs such as the barbiturates is only moderately increased in chronic users.

- § Many clinically important drug interactions result from enzyme induction, a few of which are listed in the above table.

- § Examples:

A) The antibiotic rifampin, given for 3 days, reduces the effectiveness of warfarin as an anticoagulant.

B) Conversely, enzyme induction can increase toxicity of a drug whose toxic effects are mediated via a metabolite. Paracetamol toxicity is the case: it is due to N-acetyl-p-benzoquinone imine, which is formed by cytochrome P450. Consequently the risk of serious hepatic injury following paracetamol overdose is increased in patients whose cytochrome P450 system has been induced, for example by chronic use of alcohol. It is likely that part of the variability in rates of drug metabolism between individuals results from varying exposure to environmental contaminants, some of which are strong enzyme inducers.

- § Enzyme induction can be exploited therapeutically, by administering phenobarbitone to premature babies to induce glucuronyl transferase, thereby increasing bilirubin conjugation and reducing the risk of kernicterus.

2) Enzyme inhibition

- § Drugs that may inhibit hepatic microsomal metabolism of other drugs include allopurinol, amiodarone, androgens, chloramphenicol, cimetidine, ciprofloxacin, clarithromycin, cyclosporine, diltiazem, disulfiram, erythromycin, fluconazole, fluoxetine, fluvoxamine, grapefruit juice, isoniazid, itraconazole, ketoconazole, metronidazole, mexiletine, miconazole, omeprazole, phenylbutazone. propoxyphene, quinidine, ritonavir, sulfonamides, verapamil, zafirlukast, and zileuton.

- § This can increase the action, of other drugs metabolized by the enzyme, such effects can be clinically important, examples include:

A) Interaction between the non-sedating antihistamine terfenadine and the imidazole antifungal drugs such as ketoconazole and other drugs that inhibit the CYP3A subfamily of P450 enzymes. This can result in prolongation of the Q-T interval on the electrocardiogram and a form of ventricular tachycardia in susceptible individuals.

B) Grapefruit juice inhibits CYP3A and reduces the metabolism of terfenadine and other drugs, including cyclosporin and several calcium channel antagonists.

C) Several inhibitors of drug metabolism influence the metabolism of different stereoisomers selectively. Examples of drugs that inhibit the metabolism of the active S and less active R isomers (S is 4 times more potent) of warfarin in this way are shown in the following table:

Stereoselective and non-stereoselective inhibition of warfarin metabolism
Stereoselective inhibition of clearance of S isomer 1. Phenylbutazone 2. Metronidazole 3. Sulphinpyrazone 4. Trimethoprim-sulphamethoxazole (Co-trimoxazole) 5. Disulfiram
Stereoselective inhibition of clearance of R isomer 1. Cimetidine 2. Omeprazole
Non-stereoselective inhibition of clearance of R and S Isomers Amiodarone

D) The therapeutic effects of some drugs are a direct consequence of enzyme inhibition (e.g. the xanthine oxidase inhibitor, allopurinol, used to prevent gout Xanthine oxidase metabolises several cytotoxic and immunosuppressant drugs, including mercaptopurine (the active metabolite of azathioprine), whose action is thus potentiated and prolonged by allopurinol.

E) Disulfiram, an inhibitor of aldehyde dehydrogenase used to produce an aversive reaction to ethanol, also inhibits metabolism of other drugs, including warfarin which it potentiates. Metronidazole, an antimicrobial used to treat anaerobic bacterial infections and several protozoal diseases also inhibits this enzyme, and patients are advised to avoid alcohol for this reason.

Cytochrome P-450 Isozymes: Substrates, Inhibitors, and Inducers

N.B. CYP3A4 alone is responsible for more than 60% of hhe clinically prescribed drugs metabolized by the the liver

Isozyme	Substrates	Inhibitors	Inducers
1A2	Caffeine Clomipramine (Anafranil) Clozapine (Clozaril) Flutamide (Enlexin) Imipramine (Tofranil)* Olanzapine (Zypyrexa) Tacrine (Cognex) Theophylline (Theo-Dur) Ropinirole (Requip) R-Warfarin (Coumadin) Zileuton (Zyflo)	Cimetidine (Tagamet) Ciprofloxacin (Cipro) Enoxacin (Penetrex) Ethinyl Estradiol Fluvoxamine (Luvox) Isoniazid (INH) Mexiletine (Mexitil) Norethindrone Tacrine (Cognex) Zileuton (Zyflo)	Charcoal-broiled meat Smoking
2C9	Celecoxib (Celebrex) Diclofenac (Voltaren) Dronabinol (Marinol) Flurbiprofen (Ansaid) Fluvastatin (Lescol) Glimepiride Glipizide (Glucotrol)? Glibenclamide? Ibuprofen (Motrin) Indomethacin (Indocin) Losartan (Cozaar) Montelukast (Singulair) Naproxen (Naprosyn) Phenytoin (Dilantin) Piroxicam (Feldene) Tolbutamide (Orinase) Torsemide (Demadex) S-Warfarin (Coumadin) Zafirlukast (Accolate)	Amiodarone (Cordarone) Cimetidine (Tagamet) Clopidogrel (Plavix) Co-trimoxazole (Bactrim) Disulfiram (Antabuse) Efavirenz (Sustiva) Fluconazole (Diflucan) Fluvastatin (Lescol) Fluvoxamine (Luvox) Isoniazid (INH) traconazole I (Sporanox) Ketoconazole (Nizoral) Metronidazole (Flagyl) Sulfinpyrazone (Anturane) Ticlopidine (Ticlid) Zafirlukast (Accolate)	Aminoglutethimide (Cytandren) Barbiturates Carbamazepine (Tegretol) Griseofulvin (Fulvicin) Nafcillin (Unipen) Phenytoin (Dilantin) Primidone (Mysoline) Rifampin (Rimactane)

Isozyme	Substrates	Inhibitors	Inducers
2C19	Amitriptyline (Elavil)* Carisoprodol (Soma) Citalopram (Celexa) Clomipramine (Anafranil Diazepam (Valium)* Imipramine (Tofranil)* Lansoprazole (Prevacid) Mephenytoin Pantoprazole (Protonix) Omeprazole (Prilosec) Pentamidine (Pentam) Phenytoin (minor pathway) Proguanil* Rabeprazole (Aciphex) R-Warfarin (Coumadin)	Efavirenz (Sustiva) Felbamate (Felbatol) Fluconazole (Diflucan) Fluoxetine (Prozac)* Fluvoxamine (Luvox) Omeprazole (Prilosec) Ticlopidine (Ticlid)	
2D6	Amitriptyline (Elavil)* Carvedilol (Coreg) Clomipramine (Anafranil) Codeine* Ú Morphine Desipramine (Norpramin) Dexfenfluramine (Redux) Dextromethorphan Dihydrocodeine* Efavirenz (Sustiva) Encainide Flecainide (Tambocor) Fluoxetine (Prozac)* Fluvoxamine (Luvox) Haloperidol (Haldol) Hydrocodone* Imipramine (Tofranil)* Maprotiline Methamphetamine Metoprolol (Lopressor) Mexiletine (Mexitil) Nortriptyline (Pamelor) Oxycodone (Percocet) Paroxetine (Paxil) Perphenazine (Trilafon) Propafenone (Rhythmol) Propranolol (Inderal) Risperidone (Risperdal) Thioridazine (Mellaril) Timolol (Blocadren) Tramadol (Ultram)* Trazodone (Desyrel) Venlafaxine (Effexor)	Amiodarone (Cordarone) Chloroquine (Aralen) Cimetidine (Tagamet) Diphenhydramine (Benadryl) Fluoxetine (Prozac)* Haloperidol (Haldol) Mibefradil (Posicor) Paroxetine (Paxil) Perphenazine (Trilafon) Propafenone (Rhythmol) Propoxyphene(Darvon) Quinacrine Quinidine (Quinidex) Quinine Ritonavir (Norvir) Sertraline (Zoloft) (weak) Terbinafine (Lamisil) Thioridazine (Mellaril)	**Note**: CYP 2D6 appears relatively resistant to enzyme induction.

Isozyme	Substrates	Inhibitors	Inducers
3A4	Acetaminophen (Tylenol) Alfentanil (Alfenta) Alprazolam (Xanax) Amlodipine (Norvasc) Amiodarone (Cordarone) Astemizole* Atorvastatin (Lipitor) Bepridil (Vascor) Bromocriptine (Parlodel) Buspirone (Buspar) Carbamazepine (Tegretol) Cisapride (Propulsid) Citalopram (Celexa) Clarithromycin (Biaxin) Cyclophosphamide Cyclosporine (Neoral) ¤ Dapsone Delavirdine (Rescriptor) Dexamethasone¤ Diazepam (Valium) Diltiazem (Cardizem) ¤ Disopyramide (Norpace) Doxorubicin (Adriamycin) Efavirenz (Sustiva) Ergotamine (Ergomar) Erythromycin (E-Mycin) Ethinyl Estradiol Etoposide (Vepesid) ¤ Felodipine (Plendil) Fentanyl (Sublimaze) Finasteride (Proscar) Flutamide (Eulexin) Ifosfamide (Ifex) Indinavir (Crixivan) Isradipine (DynaCirc) Itraconazole (Sporanox) Ketoconazole (Nizoral) Lidocaine Loratadine (Claritin) Losartan (Cozaar) Lovastatin (Mevacor) Methadone Methylprednisolone Mibefradil (Posicor) Miconazole (Monistat) Midazolam (Versed) Nefazodone (Serzone) Nicardipine (Cardene) ¤	Clarithromycin (Biaxin) Cyclosporine (Neoral)¤ Danazol (Danocrine) Delavirdine (Rescriptor) Diltiazem (Cardizem)¤ Erythromycin Ethinyl Estradiol Fluconazole (Diflucan) (weak) Fluoxetine (Prozac)* (weak) Fluvoxamine (Luvox) Grapefruit juice Indinavir (Crixivan) Isoniazid (INH) Itraconazole (Sporanox) Ketoconazole (Nizoral) Metronidazole (Flagyl) Methylprednisolone Mibefradil (Posicor) Miconazole (Monistat) Nefazodone (Serzone) Nelfinavir (Viracept) Norethindrone Norfloxacin (Norflox) Oxiconazole (Oxistat) Prednisone Quinidine (Quinidex) Quinine Ritonavir (Norvir) Saquinavir (Invirase) Troleandomycin (TAO) Verapamil (Calan) ¤ Zafirlukast (Accolate) Zileuton	Aminoglutethimide (Cytandren) Barbiturates Carbamazepine (Tegretol) Dexamethasone Efavirenz (Sustiva) Glutethimide Griseofulvin (Fulvicin) Nevirapine (Viramune) Phenytoin (Dilantin) Primidone (Mysoline) Rifabutin (Mycobutin) Rifampin (Rimactane) Troglitazone (Rezulin)

Isozyme	Substrates		
3A4 (cont'd)	Nifedipine (Adalat) ¤ Nimodipine (Nimotop) Nisoldipine (Sular) Nitrendipine Paclitaxel (Taxol) ¤ Pimozide (Orap) Prednisolone Quetiapine (Seroquel) Quinidine (Quinidex) Quinine Rifabutin (Mycobutin) Ritonavir (Norvir) Saquinavir (Invirase) Sertraline (Zoloft) Sibutramine (Meridia) Sildenafil (Viagra) Simvastatin (Zocor) Tacrolimus (Prograf) ¤ Tamoxifen (Nolvadex) Terfenadine* Testosterone Theophylline (minor pathway) Triazolam (Halcion) Verapamil (Calan) ¤ Vinblastine (Velban) ¤ Vincristine (Oncovin) ¤ R-Warfarin (Coumadin) Zolpidem (Ambien)		

***** = drugs with active metabolites
¤=Substrate for P-glycoprotein

3) Haemodynamic effects

§ Variations in hepatic blood flow influence the rate of inactivation of drugs that are subject to extensive presystemic hepatic metabolism (e.g. lignocaine or propranolol). A reduced cardiac output reduces hepatic blood flow, so negative inotropes (e.g. propranolol) reduce the rate of metabolism of lignocaine by this mechanism.

***IV) E*xcretion**

The main mechanisms by which one drug can affect the rate of renal excretion of another are: by inhibiting tubular secretion; by altering urine flow and/or urine pH; by altering protein binding, and hence filtration.

1) Inhibition of tubular secretion:

- § Probenecid inhibits penicillin secretion and thus prolongs its action. It also inhibits the excretion of other drugs, including azidothymidine (AZT)

Examples of drugs that Inhibit renal tubular secretion	
Drugs causing inhibition	***Drugs whose $t_{1/2}$, may be affected***
Probenecid Sulphinpyrazone Phenylbutazone Sulphonamides Aspirin Thiazide diuretics Indomethacin	Penicillin Azidothymidine Indomethacin
Verapamil Amiodarone Quinidine	Digoxin
Diuretics	Lithium
Indomethacin	Frusemide
Aspirin NSAIDs	Methotrexate

2) Alteration of urine flow and pH:

- § Loop and thiazide diuretics indirectly increase proximal tubular reabsorption of Li^+ (which is handled in a similar way as Na^+) and this can cause Li^+ toxicity in patients treated with lithium carbonate for mood disorders.

- § The effect of urinary pH on the excretion of weak acids and bases is put to use in the treatment of poisoning, but is not a cause of accidental interactions.

Important Drug Interactions

- § HP = Highly predictable. Interaction occurs in almost all patients receiving the interacting combination.
- § P = Predictable. Interaction occurs in most patients receiving the combination.
- § NP = Not predictable. Interaction occurs only in some patients receiving the combination.
- § NE = Not established. Insufficient data available to base estimate of predictability.

Drug or Drug Group	Properties Promoting Drug Interaction	Clinically Documented Interactions
Alcohol	*Chronic alcoholism results in enzyme induction. *Acute alcoholic intoxication tends to inhibit drug metabolism (whether person is alcoholic or not). *Severe alcohol-induced hepatic dysfunction may inhibit ability to metabolize drugs. *Disulfiram-like reaction in the presence of certain drugs. *Additive central nervous system depression with other central nervous system depressants.	***Acetaminophen:*** [NE] Increased formation of hepatotoxic acetaminophen metabolites (in chronic alcoholics). ***Acitretin:*** [p] increased conversion of acitretin to etretinate (teratogenic). ***Anticoagulants, oral:*** [NE] Increased hypoprothrombinemic effect with acute alcohol intoxication. ***CNS depressants:*** [HP] Additive or synergistic central nervous system depression. ***Insulin:*** [NE] Acute alcohol intake may increase hypoglycemic effect of insulin (especially in fasting patients). <u>Drugs that may produce a disulfiram-like reaction:</u> ***Cephalosporins:*** [NP] Disulfiram-like reactions noted with cefamandole, cefoperazone, cefotetan, and moxalactam. ***Chloral hydrate:*** [NP] Mechanism not established. ***Disulfiram:*** [HP] Inhibits aldehyde dehydrogenase. ***Metronidazole:*** [NP] Mechanism not established. ***Sulfonylureas:*** [NE] Chlorpropamide is most likely to produce a disulfiram-like reaction; acute alcohol intake may increase hypoglycemic effect (especially in fasting patients).

Drug or Drug Group	Properties Promoting Drug Interaction	Clinically Documented Interactions
Allopurinol	Inhibits hepatic drug-metabolizing enzymes.	***Anticoagulants, oral:*** [NP] Increased hypoprothrombinemic effect. ***Azathioprine:*** [P] Decreased azathioprine detoxification resulting in increased azathioprine toxicity. ***Mercaptopurine:*** [P] Decreased mercaptopurine metabolism resulting in increased mercaptopurine toxicity.
Antacids	*Antacids may adsorb drugs in gastrointestinal tract, thus reducing absorption. *Antacids tend to speed gastric emptying, thus delivering drugs to absorbing sites in the intestine more quickly. *Some antacids (eg, magnesium hydroxide with aluminum hydroxide) alkalinize the urine somewhat, thus altering excretion of drugs sensitive to urinary pH.	***Digoxin:*** [NP] Decreased gastrointestinal absorption of digoxin. ***Iron:*** [P] Decreased gastrointestinal absorption of iron with calcium-containing antacids. ***Itraconazole:*** [P] Reduced gastrointestinal absorption of itraconazole due to increased pH (itraconazole requires acid for absorption). ***Ketoconazole:*** [P] as itraconazole. ***Quinolones:*** [HP] Decreased gastrointestinal absorption of ciprofloxacin, norfloxacin, enoxacin (and probably other quinolones). ***Salicylates:*** [P] Increased renal clearance of salicylates due to increased urine pH; occurs only with large doses of salicylates. ***Tetracyclines:*** [HP] Decreased gastrointestinal absorption of tetracyclines.
Anticoagulants, oral	* Metabolism inducible. * Susceptible to inhibition of metabolism by CYP2C9. *Highly bound to plasma proteins. *Anticoagulation response altered by drugs that affect clotting factor synthesis or catabolism.	**1)** Drugs that may increase anticoagulant effect: ***Amiodarone:*** [P] Inhibits anticoagulant metabolism. ***Anabolic steroids:*** [P] Alter clotting factor disposition? ***Chloramphenicol:*** [NE] Decreased dicumarol metabolism (possibly also warfarin). ***Cimetidine:*** [HP] Decreased anticoagulant metabolism. ***Ciprofloxacin:*** [NE] Decreased anticoagulant metabolism?

Anticoagulants, oral (cont'd)		***Clofibrate:*** [P] Mechanism not established. ***Danazol:*** [NE] Impaired synthesis of clotting factors? ***Dextrothyroxine:*** [P] Enhances clotting factor catabolism? ***Disulfiram:*** [P] Decreased anticoagulant metabolism. ***Erythromycin:*** [NE] Probably inhibits anticoagulant metabolism. ***Fluconazole:*** [NE] Decreased warfarin metabolism. ***Gemfibrozil:*** [NE] Mechanism not established. ***Lovastatin:*** [NE] Probably decreased anticoagulant metabolism. ***Metronidazole:*** [P] Decreased anticoagulant metabolism. ***Miconazole:*** [NE] Decreased anticoagulant metabolism. ***Nonsteroidal anti-inflammatory drugs:*** [P] Inhibition of platelet function, gastric erosions; some agents increase hypoprothrombinemic response (unlikely with diclofenac, ibuprofen, or naproxen). ***Phenylbutazone:*** [HP] Inhibits anticoagulant metabolism. ***Propafenone:*** [NE] Probably decreased anticoagulant metabolism. ***Quinidine:*** [NP] Additive hypoprothrombinemia. ***Salicylates:*** [HP] Platelet inhibition with aspirin but not with other salicylates; [P] large doses have hypoprothrombinemic effect. ***Sulfinpyrazone:*** [NE] Mechanism not established. ***Sulfonamides:*** [NE] Inhibit anticoagulant metabolism; displace protein binding.

Anticoagulants, oral (cont'd)		***Thyroid hormones:*** [P] Enhance clotting factor catabolism. ***Trimethoprim-sulfamethoxazole:*** [P] Inhibits anticoagulant metabolism; displaces from protein binding. *See also Alcohol; Allopurinol.* **2)** Drugs that may decrease anticoagulant effect: ***Aminoglutethimide:*** [P] Enzyme induction. ***Barbiturates:*** [P] Enzyme induction. ***Carbamazepine:*** [P] Enzyme induction. ***Cholestyramine:*** [P] Reduces absorption of anticoagulant. ***Glutethimide:*** [P] Enzyme induction. ***Nafcillin:*** [NE] Mechanism not established. ***Phenytoin:*** [NE] Enzyme induction; anticoagulant effect may increase transiently at start of phenytoin therapy due to protein-binding displacement. ***Primidone:*** [P] Enzyme induction. ***Rifabutin:*** [P] Enzyme induction. ***Rifampin:*** [P] Enzyme induction. **3)** Effects of anticoagulants on other drugs: ***Hypoglycemics, oral:*** [P] Dicumarol inhibits hepatic metabolism of tolbutamide and chlorpropamide. ***Phenytoin:*** [P] Dicumarol inhibits metabolism of phenytoin.
Antidepressants, tricyclic and heterocyclic	*Inhibition of amine uptake into postganglionic adrenergic neuron. *Antimuscarinic effects may be additive with other antimuscarinic drugs. *Metabolism inducible.	***Barbiturates:*** [P] Increased antidepressant metabolism. ***Carbamazepine:*** [NE] Enhanced metabolism of antidepressants. ***Cimetidine:*** [P] Decreased antidepressant metabolism. ***Clonidine:*** [P] Decreased clonidine

Antidepressants, tricyclic and heterocyclic (cont'd)		antihypertensive effect. ***Guanadrel:*** [P] Decreased uptake of guanadrel into sites of action. ***Guanethidine:*** [P] Decreased uptake of guanethidine into sites of action. ***Monoamine oxidase inhibitors:*** [NP] Some cases of excitation, hyperpyrexia, mania, and convulsions, especially with serotonergic antidepressants such as clomipramine and imipramine, but many patients have received combination without ill effects. ***Quinidine:*** [NE] Decreased antidepressant metabolism. ***Rifampin:*** [P] Increased antidepressant metabolism. ***Selective serotonin reuptake inhibitors (SSRIs):*** [P] *Fluoxetine & paroxetine inhibit CYP2D6 & decrease metabolism of antidepressants metabolized by this enzyme (eg, desipramine). *Citalopram, sertraline, and fluvoxamine are only weak inhibitors of CYP2D6, but fluvoxamine inhibits CYP1A2 and CYP3A4 and thus can inhibit the metabolism of antidepressants metabolized by these enzymes (e.g. imipramine; nefazodone). ***Sympathomimetics:*** [P] Increased pressor response to norepinephrine, epinephrine, and phenylephrine.
Barbiturates	*Induction of hepatic microsomal drug-metabolizing enzymes. *Additive CNS depression with other central nervous system depressants.	***Beta-adrenoceptor blockers:*** [P] Increased β-blocker metabolism. ***Calcium channel blockers:*** [P] Increased calcium channel blocker metabolism. ***CNS depressants:*** [HP] Additive central nervous system depression. ***Corticosteroids:*** [P] Increased corticosteroid metabolism. ***Cyclosporine:*** [NE] Increased cyclosporine metabolism. ***Delavirdine:*** [P] Increased delavirdine metabolism.

Barbiturates (cont'd)		***Doxycycline:*** [P] Increased doxycycline metabolism. ***Estrogens:*** [P] Increased estrogen metabolism. ***Itraconazole:*** [P] Increased itraconazole metabolism. ***Ketoconazole:*** [P] Increased ketoconazole metabolism. ***Phenothiazines:*** [P] Increased phenothiazine metabolism. ***Quinidine:*** [P] Increased quinidine metabolism. ***Tacrolimus:*** [NE] Increased tacrolimus metabolism. ***Theophylline:*** [NE] Increased theophylline metabolism; reduced theophylline effect. ***Valproic acid:*** [P] Decreased phenobarbital metabolism. *See also Anticoagulants, oral; Antidepressants, tricyclic.*
Beta-adrenoceptor Blockers	*Beta-blockade (especially with nonselective agents such as propranolol) alters response to sympathomimetics with β-agonist activity (eg, pinephrine). *Beta-blockers that undergo extensive first-pass metabolism may be affected by drugs capable of altering this process. *Beta-blockers may reduce hepatic blood flow.	**1)** Drugs that may increase β-blocker effect: ***Cimetidine:*** [P] Decreased metabolism of β-blockers that are cleared primarily by the liver, eg, propranolol. Less effect (if any) on those cleared by the kidneys, eg, atenolol, nadolol. ***Furosemide:*** [P] Decreased metabolism of propranolol. **Hydralazine:** [P] Decreased metabolism of propranolol. **2)** Drugs that may decrease β-blocker effect: ***Enzyme inducers:*** [P] Barbiturates, phenytoin, and rifampin may enhance β-blockers metabolism; other enzyme inducers may produce similar effects. **Nonsteroidal anti-inflammatory drugs:** [P] Indomethacin reduces antihypertensive response; other prostaglandin inhibitors probably also interact.

Beta-adrenoceptor Blockers (cont'd)		**3)** Effects of β-blockers on other drugs: ***Clonidine:*** [NE] Hypertensive reaction if clonidine is withdrawn while patient is taking propranolol. ***Insulin:*** [P] Inhibition of glucose recovery from hypoglycemia; inhibition of symptoms of hypoglycemia (except sweating); increased blood pressure during hypoglycemia. ***Lidocaine:*** [NE] Decreased clearance of intravenous lidocaine; increased plasma lldocaine levels. ***Prazosin:*** [P] Increased hypotensive response to first dose of prazosin. ***Sympathomimetics:*** [P] Increased pressor response to epinephrine (and possibly other sympathomimetics); this is more likely to occur with nonspecific β-blockers.
Bile acid-binding resins e.g. cholestyramine	*Resins may bind with orally administered drugs in gastrointestinal tract. *Resins may bind in gastrointestinal tract with drugs that undergo enterohepatic circulation, even if the latter are given parenterally.	***Acetaminophen:*** [NE] Decreased gastrointestinal absorption of acetaminophen. ***Digitalis glycosides:*** [NE] Decreased gastrointestinal absorption of digitoxin (possibly also digoxin). ***Furosemide:*** [P] Decreased gastrointestinal absorption of furosemide. ***Methotrexate:*** [NE] Reduced gastrointestinal absorption of methotrexate. ***Thiazide diuretics:*** [P] Reduced gastrointestinal absorption of thiazides. ***Thyroid hormones:*** [P] Reduced thyroid absorption. *See also Anticoagulants, oral.*
Calcium channel blockers (CCB)	*Verapamil, diltiazem, and perhaps nicardipine (but not nifedipine) inhibit hepatic drug-metabolizing enzymes. *Metabolism of diltiazem, nifedipine, verapamil, and perhaps other calcium	***Carbamazepine:*** [P] ↓ carbamazepine metabolism with diltiazem & verapamil; possible ↑ in CCB metabolism. ***Cimetidine:*** [NP] Decreased metabolism of CCBs. ***Cyclosporine:*** [P] Decreased cyclosporine metabolism with diltiazem, nicardipine,

Calcium channel blockers (cont'd)	channel blockers subject to induction and inhibition.	verapamil. ***Itraconazole:*** [P] Decreased metabolism of CCBs. ***Ketoconazole:*** [P] Decreased metabolism of CCBs. ***Phenytoin:*** [NE] Increased metabolism of CCBs. ***Rifampin:*** [P] Increased metabolism of CCBs. *See also Barbiturates, Theophylline.*
Carbamazepine	*Induction of hepatic microsomal drug-metabolizing enzymes. *Susceptible to inhibition of metabolism, primarily by CYP3A4.	***Cimetidine:*** [P] Decreased carbamazepine metabolism. ***Clarithromycin:*** [P] Decreased carbamazepine metabolism. ***Corticosteroids:*** [P] Increased corticosteroid metabolism. ***Cyclosporine:*** [P] Increased cyclosporine metabolism. ***Danazol:*** [P] Decreased carbamazepine metabolism. ***Diltiazem:*** [P] Decreased carbamazepine metabolism. ***Doxycycline:*** [P] Increased doxycycline metabolism. ***Erythromycin:*** [NE] Decreased carbamazepine metabolism. ***Estrogens:*** [P] Increased estrogen metabolism. ***Haloperidol:*** [P] Increased haloperidol metabolism. ***Isoniazid:*** [P] Decreased carbamazepine metabolism. ***Itraconazole:*** [P] Decreased metabolism of carbamazepine. ***Ketoconazole:*** [P] Decreased metabolism of carbamazepine.

Carbamazepine (cont'd)		***Nefazodone:*** [NE] Decreased carbamazepine metabolism. ***Propoxyphene:*** [HP] Decreased carbamazepine metabolism. ***Selective serotonin reuptake inhibitors (SSRIs):*** [NE] Fluoxetine and fluvoxamine decrease carbamazepine metabolism. ***Theophylline:*** [NE] Increased theophylline metabolism. ***Verapamil:*** [P] Decreased carbamazepine metabolism. *See also Anticoagulants, oral; Antidepressants, tricyclic; Calcium channel blockers.*
Chloramphenicol	*Inhibits hepatic drug-metabolizing enzymes.	***Phenytoin:*** [P] Decreased phenytoin metabolism. ***Sulfonylurea hypoglycemics:*** [P] Decreased sulfonylurea metabolism. *See also Anticoagulants, oral.*
Cimetidine	*Inhibits hepatic microsomal drug-metabolizing enzymes. (Ranitidine, famotidine, and nizatidine do not appear to do so.) *May inhibit the renal tubular secretion of weak bases. *Purportedly reduces hepatic blood flow, thus reducing first-pass metabolism of highly extracted drugs. (However, the ability of cimetidine to affect hepatic blood flow has been disputed.)	***Benzodiazepines:*** [P] Decreased metabolism of alprazolam, chlordiazepoxide, diazepam, halazepam, prazepam, and clorazepate but not oxazepam, lorazepam, or temazepam. ***Carmustine:*** [NE] Increased bone marrow suppression. ***Ketoconazole:*** [NE] Decreased gastrointestinal absorption of ketoconazole due to increased pH in gut; other H_2 blockers and proton pump inhibitors would be expected to have the same effect. ***Itraconazole:*** [NE] Decreased gastrointestinal absorption of itraconazole due to increased pH in gut; other H_2-receptor antagonists and proton pump inhibitors would be expected to have the same effect. ***Lidocaine:*** [P] Decreased metabolism of lidocaine; increased serum lidocaine. ***Phenytoin:*** [NE] Decreased phenytoin metabolism; increased serum phenytoin. ***Procainamide:*** [P] Decreased renal excretion of procainamide; increased serum

Cimetidine (cont'd)		procainamide levels. Similar effect with ranitidine but smaller. ***Quinidine:*** [P] Decreased metabolism of quinidine; increased serum quinidine levels. ***Theophylline:*** [P] Decreased theophylline metabolism; increased plasma theophylline. *See also Anticoagulants, oral; Antidepressants, tricyclic; Beta-adrenoceptor blockers; Calcium channel blockers, Carbamazepine.*
Cyclosporine	*Metabolism inducible. *Susceptible to inhibition of metabolism by CYP3A4. (Tacrolimus and sirolimus appear to have similar interactions.)	***Amphotericin B:*** [NE] Possible additive nephrotoxicity. ***Androgens:*** [NE] Increased serum Cyclosporine. ***Barbiturates:*** [P] Increased Cyclosporine metabolism. ***Carbamazepine:*** [P] Increased Cyclosporine metabolism. ***Clarithromycin:*** [P] Decreased Cyclosporine metabolism. ***Diltiazem:*** [NE] Decreased Cyclosporine metabolism. ***Erythromycin:*** [NE] Decreased Cyclosporine metabolism. ***Fluconazole:*** [NE] Decreased Cyclosporine metabolism, especially with large fluconazole doses. ***Itraconazole:*** [P] Decreased cyclosporine metabolism. ***Ketoconazole:*** [NE] Increased serum cyclosporine with nephrotoxicity due to decreased cyclosporine metabolism. ***Lovastatin:*** [NE] Myopathy and rhabdomyolysis noted in patients taking both drugs. ***Nefazodone:*** [P] Decreased cyclosporine metabolism. ***Phenytoin:*** [NE] Increased cyclosporine metabolism.

Cyclosporine (cont'd)		***Rifampin:*** [P] Increased cyclosporine metabolism. ***Ritonavir:*** [P] ↓ cyclosporine metabolism. ***Verapamil:*** [NE] ↓ cyclosporine metabolism. *See also Barbiturates; Calcium channel blockers.*
Digitalis glycosides	*Digoxin susceptible to inhibition of gastrointestinal absorption. *Digitalis toxicity may be increased by drug-induced electrolyte imbalance (eg, hypokalemia). *Digitoxin metabolism inducible. *Renal excretion of digoxin susceptible to inhibition.	**1)** Drugs that may increase digitalis effect: ***Amiodarone:*** [P] Reduced renal digoxin excretion leads to increased plasma digoxin concentrations. ***Clarithromycin:*** [NE] Reduced renal excretion of digoxin. ***Diltiazem:*** [P] Increased plasma digoxin due to reduced renal clearance. ***Erythromycin:*** [NE] Reduced renal excretion of digoxin. ***Itraconazole:*** [NE] Reduced renal excretion of digoxin. ***Potassium-depleting drugs:*** [P] Increased likelihood of digitalis toxicity. ***Propafenone:*** [P] Increased plasma digoxin levels. ***Quinidine:*** [HP] Reduced digoxin excretion; displacement of digoxin from tissue binding sites; digitoxin may also be affected. ***Spironolactone:*** [NE] Decreased renal digoxin excretion and interference with some serum digoxin assays. ***Verapamil:*** [P] increased plasma digoxin levels. **2)** Drugs that may decrease digitalis effect: ***Kaolin-pectin:*** [P] Decreased gastrointestinal digoxin absorption. ***Penicillamine:*** [NE] Decreased plasma digoxin. ***Rifampin:*** [NE] Increased metabolism of digitoxin and possibly digoxin. ***Sulfasalazine:*** [NE] Decreased gastrointestinal digoxin absorption. *See also Antacids; Bile acid-binding resins.*

Disulfiram	*Inhibits hepatic microsomal drug-metabolizing enzymes. *Inhibits aldehyde dehydrogenase.	***Benzodiazepines:*** [P] Decreased metabolism of chlordiazepoxide and diazepam but not lorazepam and oxazepam. ***Metronidazole:*** [NE] Confusion and psychoses reported in patients receiving this combination; mechanisms unknown. ***Phenyloin:*** [P] Decreased phenytoin metabolism. *See also Alcohol; Anticoagulants, oral.*
Estrogens	*Metabolism inducible. *Enterohepatic circulation of estrogen may be interrupted by alteration in bowel flora (eg, due to antibiotics).	***Ampicillin:*** [NP] Interruption of enterohepatic circulation of estrogen; possible reduction in oral contraceptive efficacy. Other oral antibiotics may have a similar effect. ***Corticosteroids:*** [P] Decreased metabolism of corticosteroids leading to increased corticosteroid effect. ***Diazepam:*** [NE] Decreased diazepam metabolism. ***Griseofulvin:*** [NE] Possible Inhibition of oral contraceptive efficacy; mechanism unknown. ***Phenytoin:*** [NP] Increased estrogen metabolism; possible reduction in oral contraceptive efficacy. ***Primidone:*** [NP] Increased estrogen metabolism; possible reduction in oral contraceptive efficacy. ***Rifabutin:*** [NP] Increased estrogen metabolism; possible reduction in oral contraceptive efficacy. ***Rifampin:*** [NP] Increased estrogen metabolism; possible reduction in oral contraceptive efficacy. ***Troglitazone:*** [NP] Increased estrogen metabolism; possible reduction in oral contraceptive efficacy. *See also Barbiturates; Carbamazepine.*
HMG-CoA reductase inhibitors	*Lovastatin, simvastatin, and, to a lesser extent, atorvastatin are susceptible to CYP3A4 inhibitors & inducers.	***Clarithromycin:*** [P] Decreased statin metabolism. ***Clofibrate:*** [NP] Increased risk of myopathy.

HMG-CoA reductase inhibitors (cont'd)	*Increased risk of additive myopathy risk with other drugs that can cause myopathy.	***Diltiazem:*** [NE] Decreased statin metabolism. ***Cyclosporine:*** [P] Decreased statin metabolism. ***Erythromycin:*** [P] Decreased statin metabolism ***Itraconazole:*** [P] Decreased statin metabolism. ***Ketoconazole:*** [P] Decreased statin metabolism. ***Nefazodone:*** [NE] Decreased statin metabolism.
Iron	Binds with drugs in gastrointestinal tract, reducing absorption.	***Methyldopa:*** [NE] Decreased methyldopa absorption. ***Quinolones:*** [P] Decreased absorption of ciprofloxacin. ***Tetracyclines:*** [P] Decreased absorption of tetracyclines; decreased efficacy of iron. ***Thyroid hormones:*** [P] Decreased thyroxine absorption. *See also Antacids.*
Levodopa	*Levodopa degraded in gut prior to reaching sites of absorption. *Agents that alter gastrointestinal motility may alter degree of intraluminal degradation. *Antiparkinsonism effect of levodopa susceptible to inhibition by other drugs.	***Clonidine:*** [NE] Inhibits antiparkinsonism effect. ***Monoamine oxidase inhibitors:*** [P] Hypertensive reaction (carbidopa prevents the interaction). ***Papaverine:*** [NE] Inhibits antiparkinsonism effect. ***Phenothiazines:*** [P] Inhibits antiparkinsonism effect. ***Phenytoin:*** [NE] Inhibits antiparkinsonism effect. ***Pyridoxine:*** [P] Inhibits antiparkinsonism effect (carbidopa prevents the interaction). *See also Antimuscarinics.*
Lithium	*Renal lithium excretion sensitive to changes in sodium balance. (Sodium depletion tends to cause lithium retention.)	***ACE inhibitors:*** [NE] Probable reduced renal clearance of lithium; increased lithium effect.

Lithium (cont'd)	*Susceptible to drugs enhancing central nervous system lithium toxicity.	***Diuretics (especially thiazides):*** [P] Decreased excretion of lithium; furosemide may be less likely to produce this effect than thiazide diuretics. ***Haloperidol:*** [NP] Occasional cases of neurotoxicity in manic patients, especially with large doses of one or both drugs. ***Methyldopa:*** [NE] Increased likelihood of central nervous system lithium toxicity. ***Nonsteroidal anti-inflammatory drugs:*** [NE] Reduced renal lithium excretion (except sulindac and salicylates). ***Theophylline:*** [P] Increased renal excretion of lithium; reduced lithium effect.
Monoamine oxidase inhibitors (MAOIs)	*Increased norepinephrine stored in adrenergic neuron. Displacement of these stores by other drugs may produce acute hypertensive response. *MAOIs have intrinsic hypoglycemic activity	***Antidiabetic agents:*** [P] Additive hypoglycemic effect. ***Buspirone: [***NE] Possible serotonin syndrome; avoid concurrent use. ***Dextromethorphan:*** [NE] Severe reactions (hyperpyrexia, coma, death) have been reported. ***Guanethidine:*** [P] Reversal of the hypotensive action of guanethidine. ***Mirtazapine:*** [NE] Possible serotonin syndrome; avoid concurrent use. ***Narcotic analgesics:*** [NP] Some patients develop hypertension, rigidity, excitation; meperidine may be more likely to interact than morphine. ***Nefazodone:*** [NE] Possible serotonin syndrome; avoid concurrent use. ***Phenylephrine:*** [P] Hypertensive episode, since phenylephrine is metabolized by monoamine oxidase. ***Selective serotonin reuptake inhibitors (SSRIs):*** [P] Fatalities have occurred due to serotonin syndrome; SSRIs are contraindicated in patients taking MAOIs. ***Sibutramine:*** [NE] Possible serotonin syndrome; avoid concurrent use.

Monoamine oxidase inhibitors (MAOIs) (cont'd)		***Sympathomimetics (Indirect-acting):*** [HP] Hypertensive episode due to release of stored norepinephrine (amphetamines, ephedrine, phenylpropanolamine, pseudoephedrine). ***Tramadol:*** [NE] Possible serotonin syndrome; avoid concurrent use. ***Venlafaxine:*** [NE] Possible serotonin syndrome; avoid concurrent use. See also Antidepressants, tricyclic and heterocyclic; Levodopa.
Nonsteroidal anti-inflammatory drugs	*Prostaglandin inhibition may result in reduced renal sodium excretion, impaired resistance to hypertensive stimuli, and reduced renal lithium excretion. *Most NSAIDs inhibit platelet function; may increase likelihood of bleeding due to other drugs that impair hemostasis. *Most NSAIDs are highly bound to plasma proteins. *Phenylbutazone may inhibit hepatic microsomal drug metabolism (also seems to act as enzyme inducer in some cases). *Phenylbutazone may alter renal excretion of some drugs.	***ACE inhibitors:*** [P] Decreased antihypertensive response. ***Furosemide:*** [P] Decreased diuretic, natriuretic, and antihypertensive response to furosemide. ***Hydralazine:*** [NE] Decreased antihypertensive response to hydralazine. Methotrexate: [NE] Possible increase in methotrexate toxicity (especially with anticancer doses of methotrexate). Phenytoin: [P] Decreased hepatic phenytoin metabolism. Triamterene: [NE] Decreased renal function noted with triamterene plus indomethacin in both healthy subjects and patients. *See also Anticoagulants, oral; Beta-adrenoceptor blockers; Lithium.*
Phenytoin	*Induces hepatic microsomal drug metabolism. *Susceptible to inhibition of metabolism by CYP2C9 and, to a lesser extent, CYP2C19.	**1)**<u>Drugs whose metabolism is stimulated by phenytoin:</u> ***Corticosteroids:*** [P] Decreased serum corticosteroid levels. ***Doxycycline:*** [P] Decreased serum doxycycline levels. ***Methadone:*** [P] Decreased serum methadone levels; withdrawal symptoms. ***Mexiletine:*** [NE] Decreased serum mexiletine levels.

Phenytoin (cont'd)		***Quinidine:*** [P] Decreased serum quinidine levels. ***Theophylline:*** [NE] Decreased serum theophylline levels. ***Verapamil:*** [NE] Decreased serum verapamil levels. *See also Cyclosporine, Estrogens.* **2)** Drugs that inhibit phenytoin metabolism: ***Amiodarone:*** [P] Increased serum phenytoin; possible reduction in serum amiodarone. ***Chloramphenicol:*** [P] Increased serum phenytoin. ***Felbamate:*** [P] Increased serum phenytoin. ***Fluconazole:*** [P] Increased serum phenytoin. ***Fluoxetine:*** [P] Increased serum phenytoin. ***Isoniazid:*** [NP] Increased serum phenytoin; problem primarily with slow acetylators of isoniazid. ***Miconazole:*** [P] Increased serum phenytoin. ***Ticlopidine:*** [NP] Increased serum phenytoin. *See also Cimetidine; Disulfiram; Phenylbutazone.* **3)**Drugs that enhance phenytoin metabolism: ***Rifampin:*** [P] Decreased serum phenytoin levels.
Pimozide	*Susceptible to CYP3A4 inhibitors; may exhibit additive effects with other agents that prolong QT_c interval.	***Clarithromycin:*** [NE] Decreased pimozide metabolism. ***Erythromycin:*** [NE] Decreased pimozide metabolism ***Itraconazole:*** [NE] Decreased pimozide metabolism. ***Ketoconazole:*** [NE] Decreased pimozide metabolism. ***Nefazodone:*** [NE] Decreased pimozide metabolism.

Potassium-sparing diuretics (amiloride, spironolactone, triamterene)	*Additive effects with other agents increasing serum potassium concentration. *May alter renal excretion of substances other than potassium (eg, digoxin, hydrogen ions).	***ACE inhibitors:*** [NE] Additive hyperkalemic effect. ***Potassium supplements:*** [P] Additive hyperkalemic effect; especially a problem in presence of renal impairment. *See also Digitalis glycosides; Nonsteroidal anti-inflammatory drugs.*
Probenecid	*Interference with renal excretion of drugs that undergo active tubular secretion, especially weak acids. *Inhibition of glucuronide conjugation of other drugs.	***Clofibrate:*** [P] Reduced glucuronide conjugation of clofibric acid. ***Methotrexate:*** [P] Decreased renal methotrexate excretion; possible methotrexate toxicity. ***Penicillin:*** [P] Decreased renal penicillin excretion. ***Salicylates:*** [P] Decreased uricosuric effect of probenecid (interaction unlikely with less than 1.5 g of salicylate daily).
Quinidine	*Metabolism inducible. Inhibits CYP2D6. *Renal excretion susceptible to changes in urine pH.	***Acetazolamide:*** [P] Decreased renal quinidine excretion due to increased urinary pH; elevated serum quinidine. ***Amiodarone:*** [NE] Increased serum quinidine levels; mechanism not established. ***Kaolin-pectin:*** [NE] Decreased gastrointestinal absorption of quinidine. ***Rifampin:*** [P] Increased hepatic quinidine metabolism. *See also Anticoagulants, oral; Antidepressants, tricyclic; Barbiturates; Cimetidine; Digitalis glycosides; Phenytoin.*
Quinolone antibiotics	*Susceptible to inhibition of gastrointestinal absorption. *Some quinolones inhibit hepatic microsomal drug-metabolizing enzymes.	***Caffeine:*** [P] Ciprofloxacin, enoxacin, and, to a lesser extent, norfloxacin, inhibit caffeine metabolism. ***Sucralfate:*** [HP] Reduced gastrointestinal absorption of ciprofloxacin, norfloxacin, and probably other quinolones. ***Theophylline:*** [P] Ciprofloxacin, enoxacin, and, to a lesser extent, norfloxacin inhibit theophylline metabolism; levofloxacin, lomefloxacin, ofloxacin, and sparfloxacin appear to have little effect. *See also Antacids; Anticoagulants, oral.*

Rifampin	Induction of hepatic microsomal drug-metabolizing enzymes.	***Corticosteroids:*** [P] Increased corticosteroid hepatic metabolism; reduced corticosteroid effect. ***Itraconazole:*** [P] Increased itraconazole metabolism; reduced itraconazole effect. ***Ketoconazole:*** [NE] Increased ketoconazole metabolism; reduced ketoconazole effect. ***Mexiletine:*** [NE] increased mexiletine metabolism; reduced mexiletine effect. ***Sultonylurea hypoglycemics:*** [P] Increased hepatic metabolism of tolbutamide and probably other sulfonylureas metabolized by the liver (including chlorpropamide). ***Theophylline:*** [P] Increased theophylline metabolism; reduced theophylline effect. *See also Anticoagulants, oral; Beta-adrenoceptor blockers; Calcium channel blockers; Cyclosporine; Digitalis glycosides; Estrogens.*
Salicylates	*Interference with renal excretion of drugs that undergo active tubular secretion. *Salicylate renal excretion dependent on urinary pH when large doses of salicylate used. *Aspirin (but not other salicylates) interferes with platelet function. *Large doses of salicylates have intrinsic hypoglycemic activity. *Salicylates may displace drugs from plasma protein binding sites.	***Carbonic anhydrase inhibitors:*** [NE] Increased acetazolamide serum concentrations; increased salicylate toxicity due to decreased blood pH. ***Corticosteroids:*** [P] Increased salicylate elimination; possible additive toxic effect on gastric mucosa. ***Heparin:*** [NE] Increased bleeding tendency with aspirin, but probably not with other salicylates. ***Methotrexate:*** [P] Decreased renal methotrexate clearance; increased methotrexate toxicity (primarily at anticancer doses). ***Sulfinpyrazone:*** [HP] Decreased uricosuric effect of sulfinpyrazone (interaction unlikely with less than 1.5 g of salicylate daily). *See also Antacids; Anticoagulants, oral; Probenecid.*
Theophylline	*Susceptible to inhibition of hepatic metabolism by CYP1A2. *Metabolism inducible.	***Benzodiazepines:*** [NE] Inhibition of benzodiazepine sedation. ***Dlltlazem:*** [P] Decreased theophylline metabolism by CYP1A3.

Theophylline (cont'd)		***Clarithromycin:*** [NE] Decreased theophylline metabolism. ***Erythromycin:*** [P] Decreased theophylline metabolism. ***Fluvoxamine:*** [P] Decreased theophylline metabolism. ***Smoking:*** [HP] Increased theophylline metabolism. ***Tacrine:*** [P] Decreased theophylline metabolism. ***Ticlopidine:*** [NE] Decreased theophylline metabolism. ***Verapamil:*** [P] Decreased theophylline metabolism. ***Zileuton:*** [P] Decreased theophylline metabolism. *See also Barbiturates; Carbamazepine; Cimetidine; Lithium; Phenytoin; Quinolones; Rifampin.*

SUMMARY

Learning Objectives

•Distinguish between pharmacokinetic and pharmacodynamic drug interactions
•Identify common and clinically significant drug interactions
•Formulate appropriate alternative treatment regimens minimizing the potential for drug interactions

Outline

•General Background
•Define various pharmacokinetic drug interactions
•Define various pharmacodynamic drug interactions
•Explore some common and clinically significant drug interactions
•Discuss patient cases

Background

•Drug Interactions can be a significant cause of medication errors, adverse medication reactions, and patient morbidity and mortality
•Legal ramifications possible
•HOWEVER not all drug interactions are “bad”
–Synergy
–Altered metabolism or elimination
•Two main categories of drug interactions
–Pharmacokinetic
–Pharmacodynamic
•Other types of drug interactions can occur such as physical or chemical incompatibilities
•Drug interactions can occur with
–***Other drugs***
–Herbs/ Dietary supplements
–Foods or beverages (especially grapefruit juice or alcohol)
–Smoking

Types of Drug Interactions

•**Pharmacokinetic**

- Absorption: common with di/trivalent metals and enteral feeds
- Distribution
- Metabolism: most common type of pharmacokinetic drug-drug interaction; CP450 isoenzymes – substrate vs inducer vs inhibitor
- Excretion

•**Pharmacodynamic**

–Substance A enhances or duplicates the intended effect or adverse effect of Substance B i.e. agonist

–Substance A acts antagonistically with Substance B

Pharmacokinetic Drug Interactions

I) Absorption

–Product A binds with product B in the GI tract

•Example cholestyramine

–Most common example is chelation of agents with di/trivalent metals

•Examples **Ca, Al, Zn, Mg, multivitamins, antacids, etc. chelate products such as antibiotics in the quinolone or tetracycline family**

–Result = decreased effectiveness of both agents

–Management= separate doses (1 hour before or 2 hours after)

II) Distribution

–Least common type of pharmacokinetic interaction

–Drug-Drug interactions of this type are quite rare

–Drug-Disease state interactions more common

–If a drug is particularly hydro or lipophillic, then patients with certain disease states (CHF, CRF, obesity) may react differently

III) Metabolism

–Most common type of pharmacokinetic drug interaction

–Hepatic enzymes – **Cytochrome P 450 system** metabolizes numerous drugs

•Many different isoenzymes

–3A4, 2D6, 1A2, 2C9, and 2C19 most common

–3A4 most clinically significant

–Many drugs **induce** or **inhibit** certain hepatic enzymes

–Many drugs are **substrates** of the CP 450 system
–Drugs that **induce** this system **decrease** the concentrations of other drugs metabolized by CP 450 (results in decreased therapeutic effects)
–Drugs that **inhibit** CP450 enzymes cause **increases** in the concentrations of other drugs metabolized by CP450 (may increase risk of adverse effects)
–Note that other substances (foods like grapefruit, herbs like St. John's Wort, and smoking) can also affect CP 450
– CP 450 3A4 isoenzyme most common
•Common 3A4 inducers
–Carbamazepine
–Phenobarbital
–Phenytoin
–Rifampin

•Common 3A4 inhibitors
–Amiodarone
–Cannabinoids
–Erythromycin and clarithromcyin
–Azole antifungals
–Fluvoxamine, fluoxetine, nefazodone, sertraline, others possible
–Protease inhibitors
–Grapefruit

IV) Excretion
–Less common than metabolism or absorption
–Substance A may alter the renal (or other types of) elimination of substance B
–Example
•Probenecid competitively inhibits renal tubular excretion of many agents, resulting in reduced clearance of penicillins, cephalosporins, benzodiazepines, sulfonylureas, others

Pharmacodynamic Drug Interactions

I) Synergistic, additive, or agonist effects
–Two (or more) products may have similar mechanisms of action (MOAs), desired treatment outcomes, or adverse effect profiles
–Examples
•Lovastatin + clofibrate = decreased lipid and triglyceride profiles and increased risk of myopathy or rhabdomyolysis

•Acetyl salicylic acid (ASA) + ginkgo biloba = increased risk of bleeding (both agents have antiplatelet effects)

II) Antagonism

–Opposing MOAs, desired treatment outcomes, or adverse effect profiles

–One foot on the brake, one on the gas

–Examples

•Bethanechol (cholinergic agent) and ipratropium (anticholinergic agent)

•Heparin and protamine

•Albuterol and atenolol

Common, Clinically Significant Drug Interactions

•Antidepressants

•Anticonvulsants

•Cisapride (reverted to "investigational" drug)

•Digoxin

•Estrogens and oral contraceptives

•Statins

•Warfarin

•Non-prescription medications

Antidepressants

•Antidepressants are used by a huge portion of the population

•Drug Interaction potential varies greatly

•Although many antidepressants affect CP 450 (inhibition), different isoenzymes are affected to a different degree

•Predict AND **PREVENT** drug interactions

•Many CP 450 interactions possible

•Relative ranking of newer antidepressants based on CP 450 drug interaction potential:

–Most likely to interact:

•Fluvoxamine, fluoxetine, paroxetine, nefazodone

–Less likely to interact

•Sertraline

–Least likely to interact
•Mirtazapine, venlafaxine, citalopram

•**Use caution combining multiple agents that affect serotonin, potential result = serotonin syndrome**
–Other antidepressants
–Triptan migraine treatments
–Zyban

•**MAOIs uncommonly used, but commonly interact**
–2 week washout

Anticonvulsants

•Significant drug interactions frequently occur with anticonvulsants
•**Anticonvulsants are often used in combination, even though they may interact with each other**
–Examples: phenytoin, phenobarb, valproic acid (VA), carbamazepine
•Not necessarily a contraindication
•Monitor serum drug levels and signs & symptoms (s/sx) of adverse effects

I) Carbamazepine

•Carbamazepine can decrease the effectiveness of:
–Oral contraceptives
–Cyclosporine
–Phenytoin
–Benzodiazepines
–Valproic Acid
–Thyroid preparations
–Warfarin
–Others

•These meds can increase the concentrations and adverse effects of carbamazepine:
–Erythromycin
–INH
–Propoxyphene
–Verapamil & diltiazem
–Cimetidine (not other H2s)

II) Phenytoin

•Phenytoin may decrease the effectiveness of:
–OCs, itraconazole, mebendazole, midazolam, VA, cyclosprine, theophylline, doxycycline, quinidine, disopyramide, carbamazepine
•Phenytoin's effectiveness may be decreased by:
–Rifampin, folic acid, theophylline, antacids, sulcralfate, and some chemo
– Continuous enteral feedings as feeds bind to phenytoin, drastically decreasing absorption

•Agents which may increase phenytoin conc/toxicity:
–INH, fluconazole, ticlopidine, amiodarone, cimetidine, disulfiram, fluoxetine, sulfonamides

•Phenytoin may increase the toxicity of these agents:
–Warfarin, dopamine, barbiturates,
•Valproic acid may either increase or decrease phenytoin concentrations

III) Valproic acid (VA)

•Agents that may decrease VA concentrations:
–Carbamazepine, cholestyramine, lamotrigine

•VA may decrease concentrations/effects of:
–Phenytoin

•Agents that may increase VA concentrations:
–Cimetidine, erythromycin, salicylates (ASA)

•VA may increase concentrations/effects of:
–Tricyclic antidepressants (TCAs)

Digoxin

•Digoxin (dig)
–Many clinically significant drug interactions
–Variety of mechanisms
–If combinations unavoidable, increase monitoring of serum digoxin levels and clinical s/sx of adverse effects

•"Normal" dig levels typically range from 0.8 to 2.5 ng/ml depending on laboratory and disease state

•Remember that adverse effects to dig can occur when serum levels are within the “normal” range

•Agents that may decrease digoxin levels
–Phenytoin
–Cholestyramine (and other bile acid sequestrants)
–Neomycin
–Others

•Agents that may increase digoxin levels
–Amiodarone
–Propafenone
–Quinidine
–Verapamil
–Itraconazole
–Calcium preparations
–Cyclosporin
–Erythromycin & clarithromycin
–Tetracycline (TCN)
–Others

Estrogens and Oral contraceptives (OCs)

•Combining estrogens or OCs with the following agents may result in breakthrough bleeding or decreased effectiveness
–Carbamaxepine
–Barbiturates
–Phenytoin
–Rifampin
–TCN, ampicillin and potentially other antibiotics

•Estrogens with corticosteroids may increase steroid toxicity

Statins

•Most HMG Co A Reductase Inhibitors are significantly metabolized by be the CP450 3A4 isoenzyme and most interactions are related to 3A4 enzyme inhibition

•In addition to metabolism interactions with statins, monitor also for myopathy “synergy” and liver function tests (LFT) elevations

•**Agents commonly interacting with statins include**
–Erythromycin or clarithromycin (NOT azithromycin)

–Azole antifungals
–Protease inhibitors
–Some SSRIs including fluvoxamine, fluoxetine, sertraline, etc.
–

•**Note that pravastatin has fewer CP 450 3A4 interactions and may be preferable over other statins if trying to avoid a specific drug interaction**
–Pravastatin is no less likely to interact with other drugs causing myopathies or increased LFTs

Warfarin

•The King of Drug Interactions

•Drug-drug, drug-food, and drug-herb interactions are very common

•Narrow Therapeutic Window

•Very serious consequences
–Decreased effectiveness may result in thrombosis
–Increased risk of adverse effects, especially bleeding
•Diet needs to be consistent

•Foods high in vitamin K
–Green vegetables
–Mayonnaise
–Oils (canola & soybean)

•CAN still eat these foods, just keep similar amount in diet

•**Drugs that may decrease warfarin's anticoagulant effects**:

(Procoagulants)
–Estrogens/ OCs
–Vitamin K (MVIs)

(Decreased absorption)
–Aluminum hydroxide
–Cholestyramine et al

(Enzyme induction)
–Barbiturates
–Carbamazepine
–Griseofulvin
–Phenytoin
–Nafcillin
–Rifampin

•**Drugs that increase bleeding tendency**

(**Inhibit procoagulant factors**)
–Antimetabolites
–Quinidine
–Quinine
–Salicylates

(**Ulcerogenic drugs**)
–Corticosteroids
–NSAIDS and COX 2s to a lesser extent

•Enhanced anticoagulant effects
–Other anticoagulants, antiplatelets, thrombolytics
–Altered metabolism, etc.
•Alcohol
•Antimicrobials including quinolones, SMZ-TMP, erythromycin, -azole antifungals, metronidazole
•Phenytoin
•Disulfiram
•Cimetidine
•Others

•Many herbal products and dietary supplements can also interact with warfarin
•Remember the "**F**our **G**s"
–Feverfew
–Ginkgo biloba
–Ginseng
–Garlic
–Ginger

•Many others possible, including St. John's Wort

Non-prescription drug interactions

•Cimetidine has many drug interactions
–Note other H2 antagonists are safer options

•Cough/Cold medications – watch blood pressure

•ASA & other NSAIDS

•Antacids- watch chelation drug interactions

•Herbal products – so little is known about their safety when combined with prescription drugs

Age as a Consideration in Drug Therapy

The "Five Rights" of Drug Administration

Virtually every pharmacology book includes a section on what's called the "Five Rights of Drug Administration." Briefly, they state that before you give any drug you should make sure that you have or know the right:

- patient
- drug
- dose
- route of administration
- time of administration

Interestingly, and although this fundamental concept seems to be the epitome of common sense, superficially simple or obvious, and applicable to all health care providers who administer drugs, they are almost never mentioned to medical students. In the sections that follow, we'll address some of these issues.

• Many factors can alter a patient's responses to drugs, and sometimes you can do something about them to help normalize the drug response. One that you can't do anything about is their ***age***.

• This handout highlights some of the major age-related factors you should consider during your clinical experiences. The emphasis is on pharmacokinetics, since changes in the way an individual absorbs, distributes, metabolizes, and excretes drugs are among the key factors that affects drug responses.

• There are some data presented in this handout: some key facts and concepts that you need to know. However, a major purpose of these notes is simply to get you thinking about the ages of your patients ahead of time.

•That's so that when you get more detailed information about specific drugs you might have a better idea of how to prescribe them and monitor their effects — hopefully to optimize therapy and minimize problems as best as possible. You'll be better able to anticipate how things might change or need to be changed.

•You should also come away with the concept that although small children and older adults are “more sensitive” to the effects of many drugs — and therefore need smaller doses of drugs than a young adult, there are exceptions.

•Importantly, for drugs overall there is no precise relationship between the patient’s age and the dose of a drug that is “right.”
We’ll look at the extremes of the life-span: first, briefly, infants, neonates, and children; and then we’ll summarize some key points about the elderly.

Pediatric Patients

- Immaturity of the many processes that affect drug pharmacokinetics, and the subsequent changes of them with maturation, affects drug responses in pediatric patients.

- Although it varies with the text you consult, you’ll usually find that there are four main age groups that comprise the pediatric population (excluding preterm infants):

a) Term to 4 weeks old (neonates)
b) 1 month to 2 years old (infants)
c) 2 to 12 years old (children)
d) 12 to 18 years old (however, many drugs approved for use in adults are approved for “children” at least 12 years old)

- For the purpose of this discussion, maturation can be defined as the process(es) of acquiring functional (and structural) characteristics similar to those of the “typical adult.”

- Obviously, the body doesn’t mature in increments. It is, instead, a continuous process that can vary in speed depending on the intrinsic make-up of the individual, and on many external factors too. Various aspects of maturation continue through puberty.

- Before we look at characteristics of various age groups, particularly in the context of pharmacokinetics and maturation of pharmacokinetic processes, you might wonder when some of these processes reach the “adult” stage. Table 1 gives some insight. You should see that, on average, most of the major determinants of pharmacokinetics reach adult levels by one year of age.

Table 1. Approximate Ages at Which Selected Determinants of Pharmacokinetics Reach "Adult Levels"	
Gastric acid secretion (gastric pH) *Gastric emptying time*	3 months 6 – 8 months
Hepatic metabolism	**Overall, about 1 year**; 5 months - 5 years for some Phase I reactions; 3 – 6 months for many Phase II reactions
Renal function	**Overall, about 1 year**; 3 – 5 months to attain mature GFR; 6 – 9 months for tubular secretion to mature; 1 year for adult-level renal blood flows

I) Neonates

- Variable drug actions occur in neonates because of the biologic characteristics of newborns, including:
  a. small body mass
  b. low body fat content
  c. high body water volume
  d. greater permeability of many membranes, including those of the skin and the blood-brain barrier.

- The physiologic instability of premature infants also requires special considerations in drug therapy.

[For the purpose of this discussion, neonates are children in or younger than their first four postnatal weeks. We will not consider premature infants (< 36 weeks gestational age)]

Absorption

•In newborns, prolonged gastric transit time, variable gastric pH and enzyme function, and the absence of intestinal flora, all affect the absorption of drugs that are given orally.

•Low peripheral perfusion rates and immature heat regulating mechanisms may also interfere with absorption.

•Topical medications are absorbed more quickly, and usually more completely, through the newborn's relatively thin cutaneous barrier such that the risk of toxicity is greater.

•Drug absorption can also occur through the placenta, and therefore newborns should be evaluated for drug effects whenever the mother has received any medication.

•It's fairly common knowledge that maternal use of alcohol and nicotine, and misuse of a variety of legal or illegal drugs (e.g., cocaine, heroin) can cause a host of problems in the newborn.

•However, many drugs prescribed by a physician (properly or not) can cause problems in the neonate, regardless of whether they were used short-term or for some longer period during pregnancy.

•Drugs given to the mother for pain control or regulation of labor can pass to the fetus during labor. In addition, drugs prescribed for the mother as part of her own long-term or perinatal care can be absorbed *in utero* and affect the newborn.

•Perhaps highest on the list are anticonvulsant drugs, many of the oral hypoglycemic drugs used to manage diabetes mellitus (insulin should be used instead of them when pharmacologic control of diabetes is necessary during pregnancy), some antihypertensive drugs, and several antibiotics and anticancer agents.

Distribution

•Newborns have a low concentration of plasma proteins and a diminished binding capacity of albumin. This results in an overall decreased total plasma protein binding capacity with respect to drugs that are extensively plasma protein-bound.

•This decreased binding capacity can be responsible for some serious adverse drug effects. For example, plasma proteins can bind bilirubin. Drugs that are highly protein-bound can displace the bilirubin and so may lead to brain damage from kernicterus as a result of hyperbilirubinemia. Sulfonamide antibiotics are a prime example of this.

•In addition, immature glial development, especially evident among premature infants, permits greater permeability of the blood-brain barrier, allowing both drugs and bilirubin rapid and more complete

access to the central nervous system, leading to a heightened risk of adverse effects.

•The volume of distribution within neonatal body compartments differs greatly from the adult. Total body water content amounts to 70% to 80% of body weight in premature and newborn infants, compared with adult values of about 50% to 55%. Extracellular fluid is about 40% of total body weight — roughly twice the adult value.

•The increased body water content, coupled with the low plasma protein binding capacity of the neonate, result in an expanded volume of distribution for water-soluble drugs. A larger relative dose of such drugs may be necessary to produce the desired therapeutic effect(s).

•Conversely, the lower level of body fat in neonates may necessitate lower relative doses of lipid-soluble drugs, a portion of which otherwise would accumulate in lipid depots and temporarily be unable to cause effects.

Metabolism

•In general, hepatic drug-metabolizing enzymes are immature in the newborn and are especially ineffective in the premature neonate. After birth, metabolic capacity may rise dramatically from a low of about one-fifth to one-third the adult rate during the first weeks of life, to more than double the adult rate at three years of age.

•Because of their poor drug metabolizing capabilities, newborn infants are at high risk for drug toxicity; therefore, drug dosages need to be determined carefully. (There are exceptions to this, as noted below in a brief discussion of theophylline, a bronchodilator drug that's widely used for managing asthma in children.)

•Neonates also produce different metabolic products for some drugs than do adults, suggesting that different metabolic pathways may be present or at least predominant during maturation. Unique metabolites have been found in newborns for several drugs, including chlorpromazine (an antipsychotic drug) & theophylline.

Excretion

•Renal function is, overall, poorly developed in neonates. As a result, neonates excrete drugs more slowly.

•Newborns have a diminished ability to concentrate urine; and a lower urine pH, which also affects excretion of some compounds.

•Renal function overall approaches adult levels at the end or the first year of life. However, as noted in Table 1 above, some aspects or determinants of renal excretory function reach adult levels somewhat earlier.

II) Infants and Children

•Several physiologic factors influence drug administration to infants (5 – 52 weeks postnatal) and children (1 –12 years of age). Progressive biologic maturity and growth stabilize the body's responses to drugs until those drug responses eventually approximate those of the adult.

•As a child grows older there is an increase in body mass, a difference in body fat content, and a decrease in body water volume, all of which can influence drug absorption, distribution, metabolism, and excretion.

•In addition, anatomic barriers such as the skin and the blood-brain barrier become more effective as the infant matures. Rapid growth spurts during childhood and puberty may also affect drug response.

•Table 2, on the next page, summarizes some of the traits of infants and very young children.

Table 2. Summary: Some Physiologic Characteristics of Infants, and Their Pharmacokinetic Consequences	
Characteristic	**Consequence**
High total body water content	Expanded volume of distribution, diminished blood levels, of water-soluble drugs
Low body fat	Increased blood levels of highly lipid-soluble drugs
Increased membrane permeability, especially of skin, blood-brain barrier	Enhanced topical absorption of drugs, toxins; enhanced CNS effects of lipid-soluble drugs
Relatively lower gastric acid-secreting capacity	More complete and/or faster absorption of drugs that are completely or partially inactivated by gastric acid, or drugs that are mainly ionized at low pH
Immature body temperature regulation	May dehydrate quickly, thereby elevating concentration of drug in blood, other aqueous fluid compartments
Immature renal or hepatic function	Delayed excretion or metabolism of certain drugs (longer half-life)

Absorption

•Gastric acidity does not begin to approach adult values until about two to three months of age. This early relative lack of gastric acid contributes to exaggerated absorption of some drugs so that, for example, oral benzyl penicillin (which at older ages is inactivated by gastric acid) is well absorbed in infants.

•Gastric emptying rates reach adult levels at about 6 to 8 months.

•Barriers such as the skin and the blood-brain barrier become more effective as the infant grows, making the child *somewhat* less vulnerable to toxic effects of some drugs.

Distribution

•Protein binding of drugs generally reaches adult levels by one year of age. Before then, the relatively diminished levels of plasma proteins, coupled with a lower binding capacity of those proteins for many drugs, has clinical implications for drugs that normally tend to be normally extensively bound.

•Recall that drug molecules, while they are bound to plasma proteins, are pharmacologically inactive (and are also unable to be

excreted or metabolized). Thus, for a given total level (or concentration) of drug in the blood, a greater fraction will be unbound, and so there exists the potential for greater (if not excessive or toxic) effects.

•Children also have a relatively higher total body water content until about two years of age. Thus, to account for a greater volume of distribution of water-soluble drugs, children younger than that age may require larger doses than older children.

•Given the presence of both diminished plasma protein levels and protein binding capacity (which could warrant reduced doses of highly bound drugs), and a higher body water content (which could necessitate reduced dosages), extra care in dosing and monitoring are important.

Metabolism

•Metabolic rates in infants and children up to about two to three years of age are, in general, higher than adult values. They decline to adult rates by puberty. Therapeutic drug dosages relative to body weight may be greater for children than for adults.

•An important example is theophylline. Its dose should be individualized for each child based on body weight, with further dosage adjustments to account for individual metabolic variations. This is done, in part, bynmonitoring the child's plasma concentrations of the drug. As the child matures, hepatic enzymes may change such that the clearance of theophylline will be reduced, and further dosage adjustments probably will be needed.

Excretion

•Mature renal and hepatic function is not reached until about six to 12 months of age.

•Until then, repeat doses of drugs should be given cautiously.

•Dosages of drugs excreted largely unchanged (unmetabolized) by the kidneys, such as digoxin (for congestive heart failure) and gentamicin (an aminoglycoside antibiotic).

Dosage Adjustments

•The package inserts and other "prescriber information" sources for many drugs — particularly drugs that are used extensively in

pediatrics — will list pediatric dosage *guidelines*. You should **always** check written guidelines before deciding on a dose; indeed, you should always check an authoritative source to see whether a drug should be prescribed for a child at all, since some medications are not approved for use in patients younger than a certain age.

•Sometimes you may have to estimate pediatric dosages:

1. Some recommended adjustments are quite general (e.g., they will list recommended dosages for a rather wide range of ages).
2. The adjustments may be based solely on age, or on body weight in addition to age. But in every case they are nothing more than recommended starting points.
3. If there are impairments in drug distribution or (more likely) in disposition (metabolism and/or excretion) or due to drug-drug interactions, further adjustments will be needed, depending on the drug.

•There are several formulas that can be used to extrapolate a pediatric dose from the usual adult dose.

1. One formula is based on body surface area:

$$\text{Child's dose} = \frac{\text{body surface area (m 2)}}{1.7} \times (\text{adult dose})$$

2. Other formulae are based on the child's age or weight, such as:

Fried's Rule (for children 1 year old or younger):

$$\text{Child's dose} = \frac{\text{age in months}}{150 \text{ months}} \times (\text{adult dose})$$

Clark's Rule (for children 2 years old or younger):

$$\text{Child's dose} = \frac{\text{weight in pounds}}{150 \text{ pounds}} \times (\text{adult dose})$$

Young's Rule (for children 2 years old or older):

$$\text{Child's dose} = \frac{\text{age in years}}{(\text{age in years} + 12)} \times (\text{adult dose})$$

(The above formulae are for information only. You should be aware of their existence, but you do not need to memorize the formulae). Pediatrics text books (and pediatric therapeutics books in particular) also usually contain a nomogram that allows better estimation of pediatric doses that take into account the child's weight, body surface area, and height.

Drug Responses in Children May Differ Qualitatively, as Well as Quantitatively

• It's a common and usually correct assumption that children are "more sensitive" than a young adult to the effects of most drugs, mainly because of pharmacokinetic differences.

• An adult dose generally is simply too big: the effects of too much drug given to a child are qualitatively similar to those in an adult, only of greater magnitude.

• Nonetheless, some drugs can cause effects (and usually they are adverse effects) that are *qualitatively* different from those in adults... adverse responses that are relatively unique to children. Some of them are summarized in the following table.

Table 3. Some Adverse Drug Responses That Are "Unique" to the Fetus, Neonates, or Children

Drug	Adverse Effect
Angiotensin Converting Enzyme (ACE) Inhibitors (e.g., captopril; used mainly for hypertension or congestive heart failure)	When administered to pregnant women, may cause fatal underdevelopment of fetal renal system (kidneys, etc.)
Aspirin, other salicylates	Reye syndrome if given to some children with influenza, chickenpox, other viral illnesses
Chloramphenicol (antibiotic)	Gray syndrome when given to mother *in utero* or to neonates, infants.
Glucocorticosteroids (anti-inflammatory drugs, very effective for asthma, etc.)	Linear growth suppression with prolonged systemic administration
Hexachlorophene (topical disinfectant)	Brain damage
Phenytoin (anticonvulsant)	Gingival hyperplasia
Sulfonamides (antibiotics)	Kernicterus in neonates
Tetracyclines (antibiotics)	Staining of developing teeth (*in utero* on through development of permanent teeth)

Drug Misuse in Children

Parents or guardians are most often responsible for administering medication to infants and young children.

Management of drug therapy requires attention, coordination (who is responsible for giving medications to the child? who's turn is it today?), and some understanding of the drug(s) to be given (when to give them; how; and so on).

In many cases, young or poorly educated parents do not have the experience or knowledge to ask appropriate questions about a drug in order to clarify their understanding of the administration instructions.

Common causes of drug misuse in pediatric patients include the following. A major way to reduce the risk and incidence of these problems is education. Parents or other caregivers should be given precise and, preferably, written instructions about medicating their children. They should always be encouraged to contact a health care provider if they have questions.

1. Multiple medication dispensers (e.g., mother, father, grandmother, babysitter), resulting in the risk of duplicated or missed doses.

2. Use of incorrect prescriptions (e.g., from previous illnesses or from another child with similar symptoms).

3. Discontinuance of medication as soon as symptoms appear to be alleviated (particularly problematic with antibiotic and anticonvulsant therapy).

4. Supplementing more than one medication without the doctor's knowledge or supervision.

5. Accidental ingestion of medications (medications are a common source of poisoning in childhood).

6. Baby's ingestion of drug through mother's breast milk. (It is important for the prescriber to be aware of drugs that are excreted in breast milk, and to advise the mother accordingly as to whether to avoid breast-feeding or stop taking the drug.) Most drug references (and package inserts for all drugs) have information/advice about what to do.

7. Measurement errors, mainly with liquid dosage forms. There is considerable misunderstanding of terms such as what a "teaspoonful" means, or what a household teaspoon contains. It's assumed to be 5 mL, but spoons vary in size and capacity, and in some cases even slight errors of measurement can cause problems, whether immediately or after several doses have been given.
When measuring is critical, advise the caregiver that very inexpensive, well calibrated syringes for measuring and administering liquids are available at virtually every pharmacy.

8. Spitting or spilling medication by a resistant child, leaving parents or other caregivers uncertain about how much drug was actually ingested by the child. One assumption is that the child got little, if any of the drug, and so the response is to give another dose. Conversely, one might assume that the child consumed the entire dose, when, in fact, little was ingested. As a result, the child is underdosed.

9. Inability to assess accurately side effects that might be developing in a child as a result of drugs.
This is complicated by a child's lack of or poorly developed language and his or her inability to otherwise recognize, understand, and communicate symptoms or signs of drug-induced problems.
10. The belief — equally applied to adult patients — that "if a small dose is good, more is better."

Can the "Right" Dose for a Child be Larger than the Right Dose for an Adult?

•As surprising as it may seem, in a few (but important) instances the answer to this question is yes.
•Listed below are maximum oral daily maintenance doses for anhydrous theophylline, which is classified as a methylxanthine bronchodilator:

- At one time this drug was one of the most widely used oral bronchodilators for asthma patients of all ages. According to pulmonologist experts theophylline now ranks as a third- or fourth-line maintenance drug, especially for adults.

- Its margin of safety (the difference between average effective and average toxic blood concentrations is small.

- However, for various reasons it is still widely used, especially in pediatrics (for which asthma is still the most common cause of hospital admissions, morbidity, and mortality).

- Look at the data and notice how the general rule “children get smaller drug doses than adults” doesn’t apply.

Table 4. Typical Oral Maximum Daily Maintenance Doses of Anhydrous Theophylline, a Bronchodilator, at Various Ages*

Age	Dose per 24 hr, mg/kg
Adults, children > 16 years	13
12 – 16 years	18
9 – 12 years	20
6 months – 9 years	24
Infants (= < 6 months)	4-12

* The doses listed as “per 24 hours” are given in divided doses at specified intervals throughout the period. Further adjustments must be made based on other characteristics of the individual patient.

The average adult weighs 70 kg, so 13 mg/kg x 70 kg = 910 mg, or roughly 900 mg per day. But what would happen if you remembered that theophylline daily dosages for, say, your 6 month- to 9 year-old patient was “bigger than” the daily dose for an adult , but you forgot that “bigger than” only applied when you normalize the dose to the patient’s body weight? That is, what if you gave your 6 month- to 9 year-old patient more than 900 mg/day, instead of more than 13 mg/kg per day?

Older Adults

•Over the last 100 years the number of elderly people (age 65 and older) in our society has grown faster than the rest of the population.

•One ramification of this “graying” of society is a rapid increase in the needs and demands for health care services. For example, recent evidence indicates that the number of hospital days for elderly patients is greater than for all children aged 15 and younger.

•Older adults use a disproportionate amount of health-care services, including drugs.

•Polypharmacy, the prescribing of many drugs at one time, is common in older adults. As the number and complexity of illnesses increase with age, the complexity of drug treatment increases.

•Patients may receive medications from several different physicians, and there is no guarantee that each prescriber is aware of what the other is doing.

•Add to that the likelihood that the older patient is self-prescribing other medications for a variety of real or perceived illnesses (or actually and unknowingly to counteract some illness or discomfort caused by their prescription drugs).

•Unless they are asked specifically about drug use, this important assessment information may be unknown to the physician.

•Overall, drug-drug interactions have a major role in the adverse drug responses of older adults, and the general dissatisfaction with drug therapy (and with the health care system in general) expressed by many elders.

•Older adults take about three times the amount of drugs taken by people under age 65. On the average, elders living in the community receive from three to five drugs per day.

•Naturally, high on the list of the most commonly prescribed drugs are those used to treat:

1. Cardiovascular disorders (e.g., heart failure, hypertension)
2. CNS disorders (e.g., depression, dementia, psychosis)

3. Pain and inflammation (anti-arthritic drugs).

- Self-prescribed drugs include:
    1. Those affecting the GI tract (antacids, antidiarrheals, laxatives, and cathartics are “popular” or, at least, perceived as important an innocuous by the users).
    2. The CNS (sleep aids) drugs,
    3. Analgesic and anti-inflammatory drugs.

•Then you need to consider the potential impact of various nutritional supplements and nontraditional medications (including some of dubious value which are advertised as nutritional supplements, rather than as drugs). In most cases the biologic effects of these products are largely unknown.
We know even less about how they might interact with traditional drugs.

•In too many cases, when you are dealing with multiple disorders and a dozen or more drugs (or even a fewer number), it becomes virtually impossible to keep control of everything, avoid significant drug interactions, and prevent drug-induced side effects from becoming almost as problematic as the disorders for which they are being given.

•In too many cases, even when the only drugs taken are prescribed drugs and the number is relatively small, therapy falls far short of the goal of causing no harm.

Pharmacokinetic Changes in Older Adults

•As we grow older, drug absorption, distribution, metabolism and excretion can be altered through the combined influences of age-related physiologic changes, disease, nutrition, and drug therapy.

•The major pharmacokinetic changes are explained in the following discussion and summarized in Table 5, on the next page. All of them help explain why, in most cases, drug doses should be reduced in elderly persons, and why especially careful monitoring of therapy (and communication and coordination between multiple
•prescribers) is so important.

•A common but incorrect assumption that relates to older individuals overall, and perhaps to drug therapy in particular, is that "everything deteriorates" with age. Although many of the factors that affect pharmacokinetics do decline as one reaches the age of 65 and beyond (and some actually start to decline after the age of 50, and for some people even before then), many do not decline intrinsically. That is, many of the physiologic changes that occur as we age, and that we ascribe to aging *per se*, really don't change at all.

•Instead, the changes of such factors as cardiac output, or hepatic or renal function, occur secondary to diseases that are more common in elderly individuals. They do not reflect senescence in the truest sense.

•When thinking about how pharmacokinetic changes in the elderly might necessitate changes in drug therapy, you need to think beyond the obvious. It may be obvious, for example, that a patient will (and sometimes must) receive a drug that depends greatly on hepatic metabolism (or renal excretion) as a prime way to terminate its effects in the body, even if or when that patient has liver disease (or renal disease).

•What is not so obvious, but is so critically important to remember, is that most drugs depend on the interrelated function of several organs for their entry into, and elimination from, the body. It's naïve to believe that for the patient with a "bad liver," all one needs to do is choose an alternative but otherwise similar drug that isn't metabolized (or is metabolized much less) and administer it carelessly.

•Moreover — and this appears to be especially true for the elderly — although a particular disease may appear to alter the function of mainly one organ (e.g., the liver), other organs and organ systems, and their essential functions, can be affected too. A good example of this is heart failure, which is much more common in the elderly.

•The heart does not absorb, metabolize, or excrete drugs. However, because one of its prime functions is to deliver blood to the key absorptive, metabolizing, and excreting organs, heart dysfunction can cause a host of pharmacokinetic changes that complicate therapy. Likewise, drugs that exert a major effect on a particular organ or organ system can also have an impact on pharmacokinetic processes carried out by other organs.

•Other common age-associated conditions that can have a widespread impact on pharmacokinetics include dehydration, malnutrition, hyper-or hypotension, diabetes, and pulmonary disease.

Table 5. Summary: Some Physiologic Characteristics of Older Adults, and their Pharmacokinetic Consequences	
Characteristic	**Consequence**
Decreased body water content	Narrower distribution, increased blood levels, of water soluble drugs
Increased body fat	Decreased blood levels of highly lipid-soluble drugs
Decreased serum albumin levels	Increased free levels (and effect, metabolism/excretion) of drugs that are normally highly protein-bound
Relatively lower gastric acid-secreting capacity	More complete and/or faster absorption of drugs that are completely or partially inactivated by gastric acid, or drugs that are mainly ionized at low pH
Decreased cardiac output and local blood flow	Cardiac output falls about 30% between the ages of 50 and 65 years; splanchnic and hepatic blood flow decline by about the same amount; renal blood flow (and GFR) fall to about half their values measured at age 50. Locally reduced blood flow can reduce enteric absorption of drugs, and/or reduce drug metabolism and excretion. ***Excretory changes are the most important.***
Decreased liver mass and hepatocyte function	Decreased metabolism (and longer half-life) of drugs depending on hepatic metabolism; excessive initial effects of some drugs that normally depend on first-pass metabolism; liver mass declines about 30% between age 50 and 65.

•Finally, don't underestimate the capacity of one determinant of pharmacokinetics in the older individual to compensate for changes in another. For example, circulating levels of many hormones stay remarkably constant in the later years of life. Although hormone synthesis and release may truly be reduced, for example, changes of other factors may be sufficient to compensate

for the reduced synthesis, thereby maintaining circulating hormone levels at levels similar to those found in younger adults.

Absorption

•Of the four main pharmacokinetic factors that govern the fates and actions of drugs, absorption seems to be the least affected. (Although it might be affected least, the changes can be important nonetheless, and we will focus on absorption of drugs administered orally).

•If there are changes, they usually involve the rate at which drugs are absorbed from the GI tract. The bioavailability (extent of absorption) of oral doses is affected much less and much less often.

•Gastric pH, which affects the ionization and diffusibility of drugs, tends to increase because of decreased gastric acid secretion. There are also decreases in gut motility, surface area (at least in terms of surface area that can functionally absorb drugs well), and blood flow.

•These changes are more likely caused by disease, nutritional status, and drug therapy, than by simple age-related physiologic changes. Overall, neither the rate of drug absorption from the gut, nor the amount of a dose that is absorbed (bioavailability) is changed much.

•However, as noted below, significant age-associated decreases in hepatic metabolism (and hepatic blood flow) can make it appear as if greater amounts of some drugs have been absorbed.

Distribution

•The lean body mass of an older adult decreases by 25% to 30%. Actually, this change starts much earlier in life. Estimates indicate that women lose, on average, about 5 kg of lean body weight between the ages of 25 and 75 years. Men lose between two- and three times that much over the same time span.

•Body water content decreases, and body fat increases, with and generally in proportion to the fall of total body weight. The fraction of total body water comprised of extracellular water seems to shrink the most in parallel with declines of lean body mass.

•Plasma concentrations of water-soluble drugs are increased because the drugs are distributed throughout a smaller relative volume of body water. Plasma concentrations of lipid-soluble drugs are decreased because of distribution into a relatively greater amount of fat.

•Lean muscle mass decreases concomitant with aging and the fall of lean body mass. This contributes to an age-related fall of the basal (or resting) metabolic rate, which also affects drug metabolism and excretion. Part of the fall of basal metabolic rate that occurs with age depends on the individual's life-style: it falls much less in individuals who remain active, through exercise, and falls much more in those who have a sedentary life style.

•Serum albumin levels usually decrease in the later years, although the changes may not be as significant or consequential as was previously thought. The declines, no matter how great quantitatively, usually reflect decreases in albumin synthesis more so than albumin loss via renal tubular changes (excretion).

•Nonetheless, since many drugs tend to bind to albumin, the decreased number of binding sites will lead to a proportionately higher number of unbound and therefore pharmacologically active molecules in the circulation. As a result, greater and potentially more adverse effects may occur unless the dose is reduced properly.

•Multiple drug therapies, common in the older adult, may result in competitive displacement of some drugs from a limited number of protein binding sites, thereby increasing free blood concentrations even more.

Metabolism

•Three main factors seem to contribute to age-associated decreases in drug metabolism, mainly in the liver:

1. decreased activity of the liver's drug metabolizing enzymes.
2. decreased hepatic blood flow, which is responsible for delivering drugs to their site of metabolism.
3. decreased functional liver mass.

• Disease, altered nutritional status, and drug therapy seem to affect hepatic enzyme activity and blood flow the most.

• Decreased liver function, which can be monitored fairly well with simple blood tests (e.g. by measuring AST and ALT) has a particularly great impact on orally administered drugs that ordinarily undergo ***extensive hepatic first-pass metabolism.***

• Overall, reduced metabolism can increase the amount of some drugs that enter the bloodstream. In the case of drugs subjected to first-pass metabolism, the excessive rise of blood levels is especially important when drug therapy is initiated, i.e., before the enzyme systems become saturated after repeated dosing.

• Reduced metabolism, whether first-pass or otherwise, simultaneously decreases the rate at which drugs appear to be cleared from the bloodstream as the result of metabolism. In view of this, diminishing liver function is one more reason for advising that drug doses be reduced, and monitored much more carefully, in the older patient.

• There's not much clinical data to make quantitative assessments of age-related changes in drug metabolism in general, or with respect to specific aspects of hepatic drug metabolism.
• That's because most of the data have been collected from animal studies. Nonetheless, and clearly, "changes" in the metabolic clearance of certain drugs that depend on certain cofactors, enzymes, or enzyme families for their biotransformation occur.

• However, it isn't known for sure whether (for example)...
    - o there is an "overall loss" of hepatic enzymes;
    - o otherwise functional enzymes are damaged (e.g., by free radical-mediated attack);
    - o there may be increased synthesis of replacement enzymes with functional (drug-metabolizing) capacities lower than younger forms of the enzyme;
    - o there is a loss of enzyme cofactors; or
    - o other alterations in the hepatocytes' intracellular milieu occur.

Excretion

Reduced renal drug excretion accounts for more adverse drug effects in the elderly than any other single pharmacokinetic factor.

About two out of every three older adults have some clinically significant age-related renal function decline or dysfunction. The major changes seem to involve reduced glomerular filtration and, to a lesser extent, tubular secretion.

Renal status is usually assessed as the creatinine clearance, which can be approximated from measurements of plasma creatinine levels. Such measurements are a common part of blood tests given to most patients, and they should be checked routinely in the elderly.

Package inserts for many drugs give guidelines (note the word guidelines) about how to modify the dose or dose interval depending on the creatinine level or clearance value. You need to check these recommendations too before prescribing, and be aware that the guidelines don't replace the need for careful and often frequent assessment of the actual drug responses and of the patient overall.

Pharmacodynamic Changes in Older Adults

•The sections above discussed altered drug responses in the elderly because of pharmacokinetic changes. For example, and unusually heightened or prolonged response to a particular drug might be explained in terms of increased or prolonged blood levels due to decreased metabolism or excretion.

•However, there is also evidence that, compared with younger persons, the elderly experience greater (or lesser) response to a particular dose of some drugs even when the plasma concentration of free (active) drug is the same, and in the "therapeutic range." That is, the changed response intensity is not caused by too much (or too little) drug at active sites, but by increased or decreased responses of the target cells to the drug molecules that are there. This is a *pharmacodynamic alteration of drug response.*

•Much less is known about pharmacodynamic changes than about pharmacokinetic alterations, in part because the pharmacodynamic changes are harder to measure.

•Nonetheless, some of what is known can be helpful when adjusting drug dosages for elderly patients, when anticipating altered and sometimes unwanted effects, and when trying to understand why these changes make the patient more or less "sensitive" to the effects of a drug. What follows is a brief overview of how some of these changes are thought to come about, with examples of each.

Receptor or Other Cellular Changes

Decreased responses to some drugs may be caused by an age-related decrease in the number of receptors with which the drug must interact. This has been used to explain, for example, a relatively weaker ability of drugs like epinephrine to stimulate the heart, and a relatively weaker ability of the adrenergic blockers that can block those receptors.

In addition, age can bring about changes in the cells' second messenger systems that are needed to translate the interaction between an agonist and its receptors into the eventual pharmacologic response.

Changes in Reflexes and Other Homeostatic Mechanisms

•Drugs acting on one organ or system sometimes trigger reflexes aimed at maintaining, more or less, the status quo. However, in the elderly some of these compensatory processes can be impaired.

•This sort of control is particularly important, and common, in the cardiovascular system. For example, some antihypertensive drugs can cause an abrupt fall in blood pressure — a phenomenon called orthostatic hypotension — when the patient stands up suddenly. Normally the autonomic nervous system responds almost instantaneously to constrict blood vessels in the legs. Without this reflex, blood would tend to pool in the legs and the brain could be deprived of sufficient blood flow, even if for a moment, such that dizziness, fainting, a fall, and serious injury could occur. In the elderly, however, the protective reflexes seem to be diminished, and so the risks are increased.

Nutritional Changes

•Nutritional deficiencies can account for some altered drug responses in the elderly. For example warfarin exerts its effects in the liver by inhibiting the synthesis of Vitamin K-dependent clotting factors. An inadequate intake of Vitamin K-containing foods, therefore, can intensify the drug's main effect, leading to abnormal or excessive bleeding.

•It's important to realize that a patient need not be in a state of general, symptomatic malnutrition or malnourishment for some adverse drug effects to occur. A deficiency of just one nutrient can have significant effects on the responses to specific drugs. It is also important to assess for factors, age-related and otherwise, that could affect nutritional status.

•Things to look for include:

1. chronic diarrhea or vomiting.
2. diminished appetite or taste
3. difficulties with chewing or swallowing.

• Some problems can be caused by age, disease, psychologic factors (e.g., depression), and even by therapy with certain other drugs. It is even important to consider economic factors that could affect a patient's ability to buy and eat a proper, healthy diet.

Side Effects in the Elderly

•The consequences of diseases encountered by the elderly, or the administration of drugs used to treat them, are too numerous to discuss separately. However, we can make some generalizations about some common drug-induced side effects that are most likely to occur and be bothersome, since some of them can be caused by several of the drug groups often given to (or self-prescribed by) the elderly.

•It is important to note that without proper recognition and management, drug side effects can become so intense and bothersome (let alone dangerous) that they outweigh some of the desired therapeutic benefits. This may cause the patient to not take their drugs are recommended, or to stop therapy with one or more drugs altogether.

Antimuscarinic Effects

•Many drugs and groups of drugs cause antimuscarinic (anticholinergic, or atropinelike) effects. These are effects that occur because drugs block the muscarinic subtype of receptors for acetylcholine and parasympathomimetic drugs.

•Drugs having antimuscarinic properties that are commonly used by the elderly include mydriatics (pupil-dilating drugs), drugs used to manage symptoms of colds and hay fever (antihistamines), and drugs used for certain types of mental illnesses (e.g., antidepressants and antipsychotics).

•Antimuscarinic effects can worsen glaucoma; prostate, bowel and bladder problems; and hypotension.

Hypotension

•As noted above, several age-associated pharmacokinetic and pharmacodynamic changes occur in the cardiovascular system. These can contribute to a prolonged and or excessive lowering of blood pressure, or acute but significant (and dangerous) posture related hypotension.

•This problem is caused not only by drugs given specifically to lower blood pressure (antihypertensive drugs), but also by other drugs that may lower blood pressure as a usual side effect.

•Examples of drugs used to treat insomnia and other sleep disorders, anxiety, depression, psychosis, parkinsonism, seizure disorders, pain, and even some manifestations of common allergies or the cold and flu. And most, if not all, of these drugs can cause other relatively common and problematic side effects for the elderly, as noted next.

Sedation, Confusion, Ataxia

•The most common side effects caused by drugs with CNS depressant activity are sedation and drowsiness, confusion and disorientation, and ataxia. Some drugs, notably some of the benzodiazepines (e.g., diazepam — VALIUM) that are considered “preferred” drugs for anxiety and insomnia, can also produce short-term memory loss (amnesia) or “hangover,” depending on their individual pharmacologic profiles.

•Besides the obvious drawbacks of being drowsy, confused, or uncoordinated, there are some real and serious dangers such as those posed by driving a car, operating dangerous machinery, or even walking, in an “impaired” state.

•The problems caused by many drugs can be aggravated by consuming even small amounts of alcohol, by hypotension or dehydration, and by other factors that are more likely to occur in the elderly.

•Another risk imposed by CNS depressants is their ability to mask or mimic CNS changes that otherwise could be valuable in recognizing or diagnosing underlying disorders such as stroke, parkinsonism, Alzheimer’s, dementia, and depression.

Compliance and Noncompliance

Medication compliance and compliance (or, as known by their more politically correct alternatives, adherence and nonadherence) are important (although not unique) considerations in drug therapy of older adults.

It appears that, on average, elderly persons are no less compliant with medications than younger persons. However, for elders some causes of noncompliance may be more important or more common than they are for others, and these should be assessed for when trying to optimize drug therapy.

The majority of cases of noncompliance in the elderly are intentional.

1. Polypharmacy, a leading cause of adverse drug effects in the elderly, also makes the medication plan inherently difficult to follow. This includes use of both drugs, which may be ordered by several physicians (with the possibility for medication duplication or unrecognized interactions), and with self-prescribed drugs. Since it’s safe to assume that multiple illnesses will be linked to the prescribing of more drugs (one or more for each illness), then one can also state that multiple or advanced illnesses contribute to noncompliance

One obvious difficulty for the patient is knowing which medications to take; and when, not only with regard to the time of day but also with respect to meals or other medications that might interfere with (for example) drug absorption. The more complex the treatment

plan, the greater the chance for noncompliance, whether the compliance is intentional, unintentional, or simply unavoidable because the regimen is so complicated.

One way to minimize the problems of polypharmacy is to keep the medication regimen as simple as possible: the fewest number of drugs, and the smallest number of daily doses and administration times.

2. Financial considerations may make it difficult for the elderly person to decide whether purchasing medications (even paying for a modest co-pay) takes priority over other necessities of life (buying food, paying the rent). It can also influence a decision to self-medicate with cheaper (although not necessarily less effective) drugs instead of those that are prescribed by the physician.

Use of self-medicating drugs can cause additional problems in its own right. If you, the prescriber, are aware of (or can actually recommend and supervise their use), then you might be able to modify other aspects of drug therapy to minimize the number or severity of side effects (e.g., from drug interactions).

Of course, if you are unaware of drug use by your patient you will be clueless in many ways. One of the greatest dangers of this ignorance is a more difficult task of determining why the medication regimen you've prescribed isn't working or is causing so many problems (e.g., adverse effects). You can spend and waste much time and money juggling drugs and ordering tests if you aren't fully aware of your patient's drug taking.

The only way to find out, of course, is to ask and ask about explicitly "what drug(s) are you taking."

3. Whether because of financial reasons, a period of symptom relief, or an episode of unpleasant side effects, medications may go unused and be saved until the patient feels a need to take them again. Some medications may become outdated during this time, losing some or all of their activity by the time they are taken again.

Many patients simply feel they do not need some (or even any) of the drugs prescribed for them, or at least they don't need such high doses.

4. Physiologic changes from aging and illness can cause such problems as forgetfulness, confusion, or anorexia, which can lead to unintentional noncompliance despite the best intent to take medications as directed.

5. Special senses, physical strength, and dexterity may be impaired. Auditory problems may make it difficult to hear advice about therapy, even though the best of verbal instructions might have been given.

Visual impairments can make it difficult to read written directions or labels of medication containers, or to identify the shape, size, or color of a medication.

Altered taste (and smell) may make it difficult to distinguish one liquid medication from another that is packaged in a similar container and looks alike in other ways.

Conditions such as arthritis can make it difficult to open medication containers, most of which have child-resistant caps.

6. Habits, practices, and social or cultural beliefs held for many years, which previously kept the patient quite well, may limit willingness to comply with therapy. Some of these factors may include the use of nonprescription drugs or other remedies ("traditional" or not), or certain diets, that can have an influence on drug taking or drug responses. Such knowledge of "myself, the way I was for years,:" can make taking medications, or tolerating the side effects or essential monitoring they impose, no more acceptable than the illness for which those drugs are being taken.

7. Personal loss or grief, especially of recent onset, can be a disincentive to taking medications.

Many approaches that foster compliance and assess for it in any patient should be applied to the elderly. In addition, the unique causes of noncompliance in elders should receive special attention.

An inability to hear instructions clearly should never be an “excuse” for noncompliance, since clearly written instructions should be provided. If possible (and it’s often necessary), those instructions should be provided to another adult (friend or family member, for example) who might share in or take major responsibility for managing the therapy. Instructions written in large type can help some patients.

Given the prevalence of polypharmacy for elders, it is also important to obtain a thorough medication history, inquiring about duplicate or interacting drugs that might be prescribed by other physicians; and about nonprescription drug use, including which medications are taken, how often, and why the patient perceived the need to take them.

In some cases you can identify alternative combination drug products that would allow simultaneous administration of two medications at once; or other alternatives with longer durations of action, which would reduce the frequency with which the drug must be taken. (Of course, the disadvantage of longer-acting alternatives is that side effects or adverse responses, whether due to excessive doses or drug-drug interactions, will last longer.)

Careful assessment and planning can also gain insight into the appropriateness of dosages. Reviewing lab test results for drug levels or indicators of impaired organ function is useful, if not essential. However, lab test results should never take the place of assessing for subjective and objective evidence of desired drug effects (e.g., symptom relief), unwanted side effects and interactions, and insight into the patient’s subjective responses to medication and disease.

Don’t lose sight of the possibility that if noncompliance goes undetected as the cause of an inadequate drug response; you may assume that the drug truly is not working. As a result, you may needlessly start raising the dose, switching to another drug, or adding more drugs to boost the effects of the first one.

We'll assume (hope) that you'll give your patients adequate instructions to enhance compliance, and you'll assess for it. What if you determine they are not compliant? You'll need to figure out why, and then you'll need to work with the patient to find acceptable solutions to the noncompliance problem — you shouldn't just "automatically" change your drug therapy plan.

Case Study #1

CS is a 58 year old female who presents to your office with a 4 day history of s/sx consistent with a bacterial URI. She is otherwise healthy. Her current medications include HRT and Ca + vit D. She receives a prescription for levofloxacin 500 mg po QD. 5 days later, she calls your office because her symptoms have not subsided.

–What questions would you ask CS?
–What are possible reasons for treatment failure?
–Would you change CS's therapy? If so, how?

Case Study #2

GB is a 67 year old male with a significant asthma history. He presents to the ED with N/V, tremors, and a "racing heart." He had been stable on theophylline 300 mg PO TID, fluticasone 220 mcg BID, and albuterol PRN. He has had no changes in medication or diet recently. He stopped smoking 8 days ago. Pertinent labs indicate a theophylline level of 52 mcg/ml and K=2.8. He is experiencing sinus tachycardia.

•What is GB's diagnosis?
–How did he get to this state?

•How would you manage GB?
–Would you alter is medication regimen?
–Would you order any additional tests? If so, what/when?
–What type of follow-up would be necessary?

Case Study #3

KL is a 41 year old female who presents to the office feeling "disoriented." She states that her urinary patterns have changed (decreased.) She has also gained a couple of pounds since her last visit. She has hypertension that is well controlled with enalapril 20 mg QD and osteoarthritis that is controlled with naproxen 1200 mg QD. Her physical exam is otherwise unremarkable. Labs come back later that afternoon indicating BUN 44, SCr 3.8, & a slightly elevated K.

•Could any of her medications contributed to her acute renal insufficiency? Which one?
•Would celecoxib be less likely to contribute to renal insufficiency compared to naproxen?
•How would you manage this patient?
–How would you treat her ARI?
–How would you change her medication regimen?

Case Study #4

RL is a 78 year old female with significant CV dysfunction. She is admitted to the hospital in acute V fib. Medication include digoxin, ASA, metoprolol, calcium, and docusate. She is begun on amiodarone. Her heart rate & rhythm trend toward normal. She later develops mental status changes, N&V, and hyperkalemia. A dig level comes back 3.8 ng/ml.

–What drug interaction may have contributed to Ms RL's current status?
–How would you manage Ms. RL?
–In retrospect, would you have done anything differently with this patient?

Case study #5

XL is an obese 43 year old male with hypercholesterolemic, HTN, and atherosclerosis. His cholesterol being treated with atorvastatin 20 mg QD and his LDL is lowering nicely. His HLD is also increasing. However his triglycerides are still significantly elevated after 12 weeks of therapy. Gemfibrizil 600 mg BID is then added to his current regimen. He returns for follow up three months later and mentions that he has been having some muscle cramping/pain in his legs and asks for something for the pain.

–How would you proceed with XL's treatment?
–Would you order any labs?
–Could a drug interaction have occurred? What?
–Would a different HMG agent have been safer?

Case Study #6

•JD is a 37 year old male who is being treated with warfarin for DVT. He is stable on 5 mg of warfarin daily (INR = 2.4) and is otherwise healthy. He develops a lower respiratory tract infection and is prescribed ofloxacin 400 mg po BID for 10 days. One week later he calls the office with a profuse nosebleed that he is unable to control. He returns to the office and his INR is found to be 5.8. His dose of warfarin is held for the two doses then restarted at 2.5 mg QOD, alternating with 5 mg.

–What are potential causes of JD's change of coagulation status?
–Can you recommend a safer alternative to ofloxacin?
–What would you expect JD's INR to be next week?

Complementary and Alternative Medicine (CAM)

What Is CAM?

As defined by the American National Center for Complementary and Alternative Medicine (NCCAM), it is a group of diverse medical and health care systems, practices, and products that are not presently considered to be part of conventional medicine. While some scientific evidence exists regarding some CAM therapies, for most there are key questions that are yet to be answered through well-designed scientific studies — questions such as whether they are safe and whether they work for the diseases or medical conditions for which they are used.

The list of what is considered to be CAM changes continually, as those therapies that are proven to be safe and effective become adopted into conventional health care and as new approaches to health care emerge.

Are complementary medicine and alternative medicine different from each other?

Yes, they are different.

Complementary medicine is used together with conventional medicine. An example of a complementary therapy is using aromatherapy to help lessen a patient's discomfort following surgery.

Alternative medicine is used in place of conventional medicine. An example of an alternative therapy is using a special diet to treat cancer instead of undergoing surgery, radiation, or chemotherapy that has been recommended by a conventional doctor.

What is integrative medicine?

Integrative medicine, as defined by NCCAM, combines mainstream medical therapies and CAM therapies for which there is some high-quality scientific evidence of safety and effectiveness.

What are the major types of complementary and alternative medicine?

NCCAM classifies CAM therapies into five categories, or domains:

- *Alternative Medical Systems*

Alternative medical systems are built upon complete systems of theory and practice. Often, these systems have evolved apart from and earlier than the conventional medical approach used in the United States. Examples of alternative medical systems that have developed in Western cultures include ***homeopathic*** medicine and ***naturopathic*** medicine. Examples of systems that have developed in non-Western cultures include traditional Chinese medicine and Ayurveda.

- *Mind-Body Interventions*

Mind-body medicine uses a variety of techniques designed to enhance the mind's capacity to affect bodily function and symptoms. Some techniques that were considered CAM in the past have become mainstream (for example, patient support groups and cognitive-behavioral therapy). Other mind-body techniques are still considered CAM, including meditation, prayer, mental healing, and therapies that use creative outlets such as art, music, or dance.

- *Biologically Based Therapies*

Biologically based therapies in CAM use substances found in nature, such as **herbs**, foods, and vitamins. Some examples include dietary supplements, herbal products, and the use of other so-called "natural" but as yet scientifically unproven therapies (for example, using shark cartilage to treat cancer).

- *Manipulative and Body-Based Methods*

Manipulative and body-based methods in CAM are based on manipulation and/or movement of one or more parts of the body. Some examples include chiropractic or osteopathic manipulation, and massage.

- *Energy Therapies*

Energy therapies involve the use of energy fields. They are of two types:

- ***Biofield therapies*** are intended to affect energy fields that purportedly surround and penetrate the human body. The existence of such fields has not yet been scientifically proven. Some forms of energy therapy manipulate biofields by applying pressure and/or manipulating the body by placing the hands in, or through, these fields. Examples include qi gong, Reiki, and Therapeutic Touch.
- ***Bioelectromagnetic-based therapies*** involve the unconventional use of electromagnetic fields, such as pulsed fields, magnetic fields, or alternating current or direct current fields.

Dictionary of Terms

Aromatherapy: Aromatherapy involves the use of essential oils (extracts or essences) from flowers, herbs, and trees to promote health and well-being.

Ayurveda is a CAM alternative medical system that has been practiced primarily in the Indian subcontinent for 5,000 years. Ayurveda includes diet and herbal remedies and emphasizes the use of body, mind, and spirit in disease prevention and treatment.

Chiropractic ("ki-roh-PRAC-tic") is a CAM alternative medical system. It focuses on the relationship between bodily structure (primarily that of the spine) and function, and how that relationship affects the preservation and restoration of health. Chiropractors use manipulative therapy as an integral treatment tool.

Dietary supplements: A dietary supplement is a product (other than tobacco) taken by mouth that contains a "dietary ingredient" intended to supplement the diet. Dietary ingredients may include vitamins, minerals, herbs or other botanicals, amino acids, and substances such as enzymes, organ tissues, and metabolites. Dietary supplements come in many forms, including extracts, concentrates, tablets, capsules, gelcaps, liquids, and powders. They have special requirements for labeling. Dietary supplements are considered foods, not drugs.

Electromagnetic fields: Electromagnetic fields (EMFs, also called electric and magnetic fields) are invisible lines of force that

surround all electrical devices. The Earth also produces EMFs; electric fields are produced when there is thunderstorm activity, and magnetic fields are believed to be produced by electric currents flowing at the Earth's core.

Homeopathic medicine is a CAM alternative medical system. In homeopathic medicine, there is a belief that "like cures like" meaning that small, highly diluted quantities of medicinal substances are given to cure symptoms, when the same substances given at higher or more concentrated doses would actually cause those symptoms.

Massage therapists manipulate muscle and connective tissue to enhance function of those tissues and promote relaxation and well-being.

Naturopathic medicine is a CAM alternative medical system in which practitioners work with natural healing forces within the body, with a goal of helping the body heal from disease and attain better health. Practices may include dietary modifications, massage, exercise, acupuncture, minor surgery, and various other interventions.

Osteopathic medicine is a form of conventional medicine that, in part, emphasizes diseases arising in the musculoskeletal system. There is an underlying belief that all of the body's systems work together, and disturbances in one system may affect function elsewhere in the body. Some osteopathic physicians practice

osteopathic manipulation, a full-body system of hands-on techniques to alleviate pain, restore function, and promote health and well-being.

Qi gong ("chee-GUNG") is a component of traditional Chinese medicine that combines movement, meditation, and regulation of breathing to enhance the flow of qi (an ancient term given to what is believed to be vital energy) in the body, improve blood circulation, and enhance immune function.

Reiki ("RAY-kee") is a Japanese word representing Universal Life Energy. Reiki is based on the belief that when spiritual energy is channeled through a Reiki practitioner, the patient's spirit is healed, which in turn heals the physical body.

Therapeutic Touch is derived from an ancient technique called laying-on of hands. It is based on the premise that it is the healing force of the therapist that affects the patient's recovery; healing is promoted when the body's energies are in balance; and, by passing their hands over the patient, healers can identify energy imbalances.

Herbology

Historical Context of Herb Usage

- Physical evidence dates back 60,000 years
- All cultures have traditions of herb use for healing
- 2000 BC - First known *Materia Medica* in Samaria
- 1st Century - Chinese *Materia Medica*
- 25% of prescription drugs derived from plants
- 80% of world population uses herbal medicine for primary care
- Herbal remedies fall into the category of complementary medicine.
- Misconceptions regarding their safety and efficacy are common.
- The fact that a substance is natural does not guarantee safety.
- Patients should know about compatibility and possible interactions when taking herbs and drugs simultaneously.
- Crude herbs are not regulated for purity and potency therefore drug – herb interactions can be caused by impurities e.g. allergens, pollens, spores; or there might be a batch to batch variability.

Summary on Some Important Medicinal Herbs

Ehinacea (purpurae; pallida; augustifolia)

A- **Chemical constituents**: root extract of E. pallida contains.

1- Flavonoids.

2- Lipophilic constituents.

- alkamides.
- polyacetylenes.

3- Hydrophilic constituents.

- echinoside.
- chicoric acid.
- caffeic acid.
- H_2O sol polysaccharide.

N. B. Alkamides, chicoric acid & H_2O soluble polysaccharides give the herb the immune modulating properties.

B- <u>Pharmacology :</u>

1. Immune modulation (↑ phagocytosis).
2. Anti – inflammatory (↓ COX & 5- LOX).

C-<u>Uses:</u>

1. Enhance immunity in upper respiratory tract infection (cold and flu).
2. Might enhance hematologic recovery following chemotherapy (investigationally).
3. Adjunct in treatment (tx) of U.T. infection.

D-<u>Adverse Effects:</u>

1. Flu like symptoms.
2. GI upset – hepatotoxicity specially if given with hepatotoxic drugs.
3. Headache – dizziness.
4. Occasionally allergic reactions.

E- Drug – drug interactions (DDI):

1- + Immunosuppressants ⟶ ↑ immunesystem ⟶ counteracts drugs' effects.

N.B. if taken > 8 weeks (not recommended) ⟶ immunosuppressent enhance drugs' effects.

2- + hepatotoxic drugs e.g. methotrexate or ketoconazole ⟶ ↑ hepatotoxicity.

F- Dosing 900 mg / d (Pallida root extract).

Feverfew (Tanacetum parthenium)

A- Chemical constituents:

1- Flavonoids.

2- Monoterpenes (e.g. camphor).

3-Sisquiterpenes: parthenolide.

a- 1^{ary} active ingredient.

b- Found in seeds & leaves.

c- Mechanism of action: bind covalently to thiol group of proteins.

d- Feverfew products should contain not less than 0.2 % parthenolide.

e- Prolonged storage ⟶ polymerization of parthenolide.

B- Pharmacology:

1- Migraine.

a- Used for prophylaxis: Parthenolide ↓ 5–HT release from platelets. In vitro ⟶ ↓ platelet aggregation.

2- Anti – inflammatory ⟶ ↓ PGs, thromboxane, LTB_4, cytokines (TNFα & I L – 1) ⟶ can be used in rheumatoid arthritis.

3- Other actions:

a- ↓ histamine release.

b- Antimicrobial against G + bacteria.

C- Uses:

1- Prophylaxis against migraine.

2- Menstrual problems.

D- Adverse effects:

1- Mouth ulcers.

2- GI upset.

E- DDI:

1- + Anticoagulants or + antiplatelets ⟶ additive ↑ bleeding risk.

2- + NSAIDs ⟶ ↓ herb effects in migraine tx.

3- + Fe ⟶ tannin content in herb ↓ Fe absorption.

F- Dosing :

2-3 fresh leaves or 125 mg/d dried leaf formulations.

Garlic (Allium sativum)

A- <u>Chemical constituents</u>

- Active ingredients are organosulfur compounds e.g. Allicin (responsible for odor of garlic)

Alliin $\xrightarrow{\text{allinase}}$ Allicin

↑ Temp + ↓ PH ⟶ allinase degradation

\ Give as enteric coated to prevent enzyme degradation.

B- <u>Pharmacological effects & uses</u>

1. CV effects:

a. Allicin ⟶ ↓ HMG Co-reductase.
b. Antiplatelet effect
c. Antioxidant action
d. Beneficial in atherosclerosis.

2. Endocrine effects:

Hypoglycemic effect.

3. Antimicrobal actions:

Allicin ⟶ active against bacteria (G+, G-); fungi (candida albicans); protozoa (entamoeba histolytica).

Mechanism: ↓ thiol-containing enzymes needed by the organism.

4. Antineoplastic effects:

a. ↓ procarcinogens for colon, esophageal, lung, breast, stomach cancer.

Mechanism: Detoxification of carcinogens & ↓ carcinogen activation

C- <u>Adverse effects:</u>

1. Nausea
2. Hypotension
3. Allergy
4. Bleeding (rare).

D- <u>DDI:</u>

1. + Anticoagulants, antiplatelets ⟶ additive effect.
2. + Hypoglycemic drugs ⟶ hypoglycemia

E- <u>Dosage:</u>

- Products should contain 1.3 % alliin.
- Enteric-coated formulations are recommended.
- 600-900 mg/d powdered garlic (equivalent to ½ -1 bulb of raw garlic.

Ginko (Ginko biloba):

A- <u>Chemical constituents:</u>

- Should contain 24% flavonoids, 6% terpens.
- Extract is prepared from leaves
- Active ingredients:

1. Flavonoids.
   - Ginkolides A, B, C, I
   - Bilobalide

2. Terpenoids

B- Pharmacological effects & uses:

1. CV effects:

a. ↑ blood flow, ↓ blood viscosity (antiplatelet activity), enhancement of endogenous NO.

- Used in intermittent claudication (120 mg/d).

2. Metabolic effects:

a. Antioxidant and radical scavenging properties (Flavonoid action).

- ↓ Markers of oxidative stress in patients undergoing coronary artery by-pass surgery.

3. CNS effects:

a. Ginko for 3-4 weeks in animals ⟶

(i) ↑ M, α_2, 5-HT_{1A}, ↓ β receptors densities.

(ii) ↑ Serum levels of Ach, NE & ↑ synaptic reuptake of 5-HT.

(iii) ↓ MAO – A & B, ↑ GABA levels.

- Used in tx of:
    (i) Cerebral insufficiency.
    (ii) Dementia of Alzheimer type.

4. Miscellaneus effects:

a. Ginkgolide B ⟶ PAF antagonism ⟶ antiplatelet & anti-inflammatory effects.

b. Studied in:

(i) Allergic & asthmatic bronchoconstriction.

(ii) Erectile dysfunction.

(iii) Tinnitus, hearing loss.

(iv) Memory loss in young patients

(v) Muscular degeneration

- Insufficient evidence to warrant clinical use.

C- <u>Adverse effects:</u>

1. Bleeding
2. Nausea, headache, diarrhea, anxiety.

D- <u>DDI:</u>

1. +Antiplatelets, anticoagulants ⟶ additive bleeding risk
2. +Anticonvulsants ⟶ ↓ drug effect ⟶ seizures
3. +Tricyclic antidepressants (TCA) or drugs which ↓ seizure threshold ⟶ risk of seizures
4. +MAOI ⟶ ↑ risk of manic episodes, headache, tremors.
5. +Garlic ⟶ bleeding risk

E- <u>Dosing:</u>

- Dried extract (containing 24% flavone glycosides, 6% terpene lactones).
- 120-240 mg/d of dried extract.
- In 2-3 doses.
- Onset after 2-4 weeks.

Ginseng (Panax ginseng, Panax quinquefolium)

A- <u>Chemical constituents:</u>

1. Active Ingredients: ***Ginsenosides*** (panaxoside)
    a. Triterpenoid saponin glycoside.
    b. Highest concentration in the plant root.
    c. Formulations should contain 7% ginsenosides.
2. Flavonoids, polysaccharides, others.

B- <u>Pharmacological effects and uses:</u>

1. Ergogenic (energizing) activity.
2. Nootropic (mind- enhancing activity).
3. Anti-stress.
    - Used to:

    a. Improve physical + mental performance.

    b. Provide resistance to stress.

    c. Enhance immune function.
4. Anti-inflammatory; antiplatelets.
5. Analgesia.
6. Improved glucose homeostasis, but ⟶ hypoglycemia

C- <u>Adverse effects:</u>

1. Estrogenic effects ⟶ mastalgia, vaginal bleeding.
2. CNS stimulations ⟶ insomnia nervousness.
3. Hypertension if high doses (> 3g/d) are used.

D- <u>DDI:</u>

<u>N.B.</u> Be cautious in patients taking, psychiatric, estrogenic or hypoglycemic medications.

1. + MAOI (e.g. Phenelzine), or neuroleptics ⟶ manic behavior.
2. +Estrogen or corticosteroids ⟶ ↑ adverse effects of the drugs.
3. +Hypoglycemics ⟶ hypoglycemia.
4. +Anticoagulants, antiplatelets ⟶ bleeding.
5. +Digoxin ⟶ ↑ drug concentration.
6. +Drugs which cause gynecomastia e.g. digoxin, spironolactone, methyldopa phenothiazines ⟶ additive effect (herb contains estrone, estroil, estradoil).
7. +Opioids ⟶ ↓ opioid effectiveness.

E- <u>Dosing:</u>

1. 1-2 g/d crude Panax ginseng root (1g is equivalent to 200 mg extract).

F- <u>Siberian ginseng</u> *(Eleutherococcus senticosus)*:

1. Not a Panax.
2. Active ingredient is eleutherosides.
3. Used to improve endurance.
4. +Digoxin ⟶ ↑ drug levels.
5. ↑ Blood pressure ⟶ contra-indicated in hypertension.
6. Dose 2-3 g/d of crude root.

Kava (Piper methpsticum)

A- <u>Chemical constituents:</u>

- Kava root contains the active ingredients:

1. Kavalactones (kavapyrones) e.g. Kawain (kavain), methysticin, yangonin.

B- <u>Pharmacological effects:</u>

1. CNS effects:

a. Drowsiness, Sedation

Mechanism: unknown, could be:

(i) ↑GABA- A receptors.

(ii) ↑ Number of GABA binding sites.

(iii) ↓ Glutamate release.

(iv) ↓ NE uptake or DA antagonism.

b. Mild anticonvulsant in animal

Mechanism: could be prolonged inactivation of voltage dependent sodium channels.

c. Analgesia.

Mechanism: could be ↑ opioid receptors.

2. Antiplatelet effect:

Kavain ⟶ ↓ COX.

C- <u>Uses:</u>

1. Anxiety + sleep disorders

- Slow onset (4-8 weeks).
- Not in patients with acute symptoms of anxiety or panic attacks.

D- <u>Adverse effects:</u> (Mild at recommended dose)

1. Tingling in mouth and GI upset.
2. Sedation, euphoria, visual & auditory changes.
3. Psychologic dependence, no reports on physiologic dependence.
4. May alter uterine tone ⟶ not in pregnancy, kavalactones are excreted in milk ⟶ not in lactation.
5. Dystonic extra pyramidal reaction (torticollis, oculogyric crisis, painful twisting trunk movements) ⟶ not in Parkinsonism.
6. Skin rash, facial swelling, photosensitivity *(reversible on drug cessation)* with chronic consumption.

E- <u>DDI:</u>

1. +CNS depressants (alcohol, antipsychotics, benzodiazepines) ⟶ additive sedative effects.
2. +Cimetidine ⟶ disorientation.

F- <u>Dosing:</u>

1. Anxiolytic:

50-70 mg tds of purified kavalactones (equivalent to 100 – 250 mg tds of dried kava root).

2. Hypnotic:

180 – 210 mg kavalactones 30 min. before bedtime.

N.B. Use should be limited to no more than 3 months to minimize dependence.

Milk Thistle (Silybum marianum)

A- Chemical constituents:

- Fruit and seeds contain lipophilic flavonolignans (Silymarin)
- Silimarin Comprises 3 isomers:

1. Silybin:
    a. Most potent
    b. Most prevalent.
    c. 50% of silymarin complex.
2. Silychristin.
3. Silydianin.

B- Pharmacological effects:

1. Liver disease:

a. ↓ Hepatic injury by Amanita mushrooms, galactos amine, carbon tetrachloride, paracetamol, ethanol.

Mechanism:

- ↓ Lipid peroxidation.
- Free radical scavenger.
- ↑ Glutathione levels.
- ↓ CYP $2E_1$ (involved in free radical generation).

b. Anti-inflammatory:

Mechanism:

- Silybin ↓ lipoxygenase enzyme ⟶ ↓ LT formation

N.B. PG formation is inhibited in doses exceeding in vivo dosing capabilities ∴ silybin reduces inflammation without affecting the cytoprotective effects of PGs

- Silybin ⟶ ↓ leukocyte migration ∴ can control acute inflammation.

c. ↑ Protein synthesis and hepatic cellular regeneration in diseased but not malignant cells.

Mechanism: ↑ RNA polymerase I activity in non malignant hepatocytes only.

d. In hepatic cirrhosis ⟶ ↓ collagen accumulation.

Mechanism: ⟶ ↓ expression of profibrinogenic cytokine TGF-β.

e. May be beneficial in management of hypercholesterolemia and gallstones (↓ bile saturation index).

Mechanism: ⟶ ↓ liver cholesterol synthesis (evidenced by ↓ biliary cholesterol concentration).

2. Chemotherapeutic effect:

a. In murine models of skin cancer, milk thistle produced ⟶ ↓ tumor initiation + promotion.

b. In human breast & prostate cancer cell lines, it produced ↓ cell growth and proliferation by including a G_1 cell cycle arrest.

C- Uses:

Milk Thistle may be effective in improving survival and liver functions in:

1. Tx of acute and chronic viral disease.
2. Tx of alcoholic liver disease.
3. Tx of toxin-induced liver injury. Parentral silybin is used in Europe as an antidote for Amanita mushroom poisoning.

D- Adverse effects:

1. Loose stools with high doses.

E- DDI:

1. +Hypoglycemic drugs ⟶ hypoglycemia
2. +Saquinavir ⟶ ↓ effectiveness of the drug.

F Dosing:

200-400 g/d (calculated as silybin) in 3 divided doses.

St. John Wort (Hypericum peforatum): natural antidepressant

A- Chemical constituents: Extract from flower contains:

1. Hypercinin (MAOI).
2. Hyperforin. 3. Others.

(1& 2 are the antidepressant constituents).

B- <u>Pharmacological effects & uses:</u>

1. Antidepressant action:

a. Hypericin ⟶ ↓ MAO – A & – B.

b. Hyperforin ⟶ ↓ uptake of NE, 5-HT & DA.

c. Extract ⟶ upregulation of 5-HT receptors.

Used in mild to moderate depression, side effects are < those of tricyclic antidepressants (TCA).

2) Antiviral and anti carcinogenic effects:

a. Parentral hypericin not the herb as a whole (photoactivated just before administration) :

i. ↓ viruses e.g HIV (used IV)

ii. ↓ growth of cells in some neoplastic tissues (given intra-lesional)

Mechanism:

1. ↓ Protein kinase – C.
2. ↓ singlet oxygen radical generation

C- <u>Adverse effects:</u>

1. Photosensitivity in the form of:

a. Elevated, itchy, erythematous lesions

b. Neuropathy associated with sun exposure (reversible), due to demyelination of cutaneous axons caused by photo activated hypericins

2. Confusion, dizziness, fatigue

3. Dry mouth, GI disturbances. 4. Allergic reactions

D- <u>DDI :</u>

1. + Anti depressants: MAOI or SSRI (e.g. paroxetine) ⟶ serotonin syndrome or hypertensive crisis
2. + Ma Huang, pseudoephedrine, yohimbine ⟶ hypertensive crisis
3. + Warfarin ⟶ ↓ drug effects (herb is enzyme inducer)
4. + Digoxin or theophylline ⟶ ↓ drugs bioavailabilities
5. + Fe ⟶ tannin content of herb ↓ Fe absorption
6. + Photosensitizers e.g piroxicam , omeprazole , sulfa ⟶ ↑ risk of photosensitivity
7. + Cyclosporin + indinavir ⟶ ↓ blood levels of the drugs
8. + Benzodiazepines ⟶ ↓ effectiveness of the drugs, ↑ side effects e.g drowsiness

E- <u>Dosing:</u>

- 900 mg/d of dried extract in three divided doses
- Onset may take 2-4 weeks

Saw Palmetto (Serender repens)

A- <u>Chemical constituents:</u>

- Active ingredients in herb berries:

Phytoserols (β-sitosterol), falvonoids, aliphatic alcohols.

- Lipophilic standardized dried extracts contain 85 – 95% fatty acids and sterols.

B- <u>Pharmacological effects & uses:</u>

1. In vitro:
    a. ↓ 5α – reductase enzyme (finasteride is the commonly used inhibitor) this enzyme is responsible for formation of dihydro-testosterone (DHT) from testosterone
    b. ↓ Binding of DHT to androgen receptors
    c. Blockade of α_1 receptors
    d. ↓ prostatic growth factors
2. In patients with benign prostatic hyperplasia
    a. ↓ nocturnal day time urinary frequency
    b. ↑ peak urinary flow
    c. Finasteride is better in reducing prostate volume but causes sexual dysfunction to a greater extent
3. The herb is used in tx of benign prostatic hyperplasia

C- <u>Adverse effects :</u>

1. Hypertension, headache, abdominal pain
2. ↓ Libido , impotence

D- <u>DDI:</u>

1. + Fe ⟶ tannin content ↓ Fe absorption
2. + Estrogen ⟶ additive effects

E- <u>Dosing:</u>

160 mg/bds orally of the standardized dried extract

Ma Huang (Ephedra species)

A- Chemcial constituents :

Active ingredients

Ephedrine

B- Uses:

1. Weight loss (in herbal weight loss products)
2. Bronchodilator in asthma
3. Enhancement of athletic and body building efforts
4. Induction of euphoric state and heightening of awareness and sexual sensations " herbal ecstasy "

C- Adverse effects:

1. CNS : Insomnia , nervousness, tremors , headache , seizures
2. CVS: hypertension, arrhythmias ischemic heart diseases, stroke, death.
3. Risk of renal stones

D- DDI:

1. + Decongestants ⟶ hypertensive crisis
2. + Methyldopa ⟶ counteracts drug action
3. + β– blockers ⟶ counteracts drug action
4. + MAOI ⟶ ↑ risk of hypertensive crisis
5. + theophylline ⟶ ↑ CNS stimulation & risk of seizures
6. + St. John's wart (MAOI) ⟶ ↑ risk of hypertensive crisis

E- <u>Dosing:</u>

- 8 mg/6hrs (24 mg/d)
- Should be given with the following warnings :

1. Not > 7 days and don't exceed the recommended dose or else ⟶ adverse effects (MI, stroke, seizures, death).

2. Contra indicated in patients with hypertension, hyperthyroidism, diabetes, seizure disorders, psychiatric conditions, glaucoma, prostatic enlargement, cardiac problems.

Tumeric See table page 35

Capsicum See table page 28

Cascara See table page 28

Chamomile See table page 28

Evening primrose See table page 29

Licorice See table page 32

Senna See table page 33

Grape seeds See table page 35

Cranberry See table page 35

Yohimbine See table page 35

Psyllium See table page 33

Royal Jelly See table page 37

Selected Herbs, Clinical Indications, Herb-Drug Interactions

HERB	COMMON INDICATION	DRUG	POTENTIAL EFFECT
Alfalfa (*Medicago sativa*)	Multiple, including treatment of arthritis, asthma, dyspepsia, hyperlipidemia, and diabetes	Anticoagulants	Contains coumarin constituents and vitamin K; excessive use can interfere with drug therapy
***Aloe** vera* latex	Strong cathartic	Cardiac glycosides, Thiazide diuretics	Can cause electrolyte imbalance and hypokalemia; May potentiate drug toxicity
Angelica (*Angelica archangelica*)	Loss of appetite, peptic discomfort	Anticoagulants	Contains coumarin constituents; may potentiate drug effect
Bearberry Uva-Ursi (*Arctostaphylos uva-ursi*)	Urinary tract antibacterial, astringent, diuretic	Urinary acidifiers, Cranberry Juice Diuretics NSAIDs	Inactivated by urinary acidifiers; active compound released only in alkaline urine. Decreased drug effect Increased gastrointestinal irritation
Black cohosh Baneberry, bugwort, Squawroot, Rattleroot (*Cimicifuga racemosa*)	Hot flashes, premenstrual discomfort and dysmenorrheal	Estrogens, Oral contraceptives Antihyperlipidemics	Herb affects hypothalamus-pituitary system, decreases luteinizing hormone secretion and binds estrogen receptors May decrease response to estrogen Possible additive effect
Borage (*Borago officinalis*)	Anti-inflammatory, sedative	Anticoagulants, Antiplatelet agents Anxiolytics	May prolong bleeding time Additive sedation
Bromelain (*Ananas comosus)*	Acute post-operative and post-traumatic swelling	Antiplatelet agents	Increased risk of bleeding

HERB	COMMON INDICATION	DRUG	POTENTIAL EFFECT
Capsicum (*Capsicum frutescens, C. annum)*	Shingles, trigeminal and diabetic neuralgia	Monoamine oxidase inhibitors _____ Antiplatelet agents	Herb increases secretion of catecholamines, increases risk of hypertensive crisis _____ Increased fibrinolytic activity, may prolong bleeding time
Cascara Bitter bark (*Rhanmus purshiana, Cascara sagrada*)	Stimulant laxative	Cardiac glycosides, Thiazide diuretics	Can cause electrolyte imbalance and hypokalemia; May potentiate drug toxicity
Chamomile (*Matricaria recutita)*	Mild sedative, antispasmodic and antiseptic agent	Iron _____ Anticoagulants	Tannin content in herb may inhibit iron absorption _____ Herb contains coumarin constituents; May increase the risk of bleeding
Chaste tree berry (*Vitex agnus-castus)*	Menstrual disorders	Dopamine receptor antagonists (i.e., phenothiazines)	Herb has dopaminergic effect, may antagonize drug effect
Dong Quai (*Angelica polymorpha, A.dahurica, A.atropurpurea)*	Menstrual disorders	Anticoagulants, Antiplatelet agents _____ Estrogens	Herb contains coumarin constituents; Possible additive drug effect _____ Herb contains phytoestrogens; May result in estrogen excess
Echinacea (*Echinacea augustifolia, E.pallida)*	Cold, flu	Immunosuppressants _____ Drugs that can damage the liver e.g. Amiodarone, Anabolic steroids, Ketoconazole, Methotrexate	Short-term use: Stimulates the immune system (phagocyte production stimulated), counteracts drug effect; Chronic use (>6-8 wk): immunosuppressive, enhances drug effect. _____ Increased risk of hepatotoxicity

HERB	COMMON INDICATION	DRUG	POTENTIAL EFFECT
Evening primrose (*Oenothera biennis)*	Lower serum cholesterol, atopic eczema	Phenothiazines, anticonvulsants	Increased risk of seizures in patients taking drug known to lower seizure threshold
Feverfew (*Tanacetum parthenium)*	Migraine, fever, menstrual problems	Anticoagulants Antiplatelet agents NSAIDs Iron	Additive anticoagulant, antiplatelet effects; Increased risk of bleeding Decreased herbal effect Tannin content in herb may inhibit Iron absorption
Garlic (*Allium sativum)*	Hyperlipidemia	Anticoagulants Antiplatelet agents Hypoglycemic drugs	Inhibits platelet aggregation; Additive anticoagulant, antiplatelet effects May potentiate drug effect causing hypoglycemia
Ginger		Anticoagulants	May increase risk of bleeding
Ginkgo (*Ginkgo biloba)*	Varicose veins, intermittent claudication, dementia, vertigo, tinnitus, SSRI-induced sexual dysfunction, cerebral vascular insufficiency	Anticoagulants Antiplatelet agents Anticonvulsants Tricyclic antidepressants, other drugs that decrease seizure threshold Monoamine oxidase inhibitors (MAOIs)	Inhibits platelet aggregation, may have additive anticoagulant, antiplatelet effects May increase risk of seizures, decrease drug effect Increased risk of seizure Ginko may intensify the effects of these drugs & increase the risk of side effects e.g. headache, tremors & manic episodes

HERB	COMMON INDICATION	DRUG	POTENTIAL EFFECT
Ginseng Asian ginseng (*Panax ginseng, P.quinquefolium)*	Normalize the body, and provide resistance to stress	Hypoglycemic drugs. Furosemide Digoxin Monoamine oxidase inhibitors Anticoagulants, antiplatelet agents Estrogens, corticosteroids Drugs that cause gynecomastia (e.g., calcium channel blockers, cardiac glycosides, methyldopa, phenothiazines, spironolactone) Opioids	Herb has hypoglycemic effect Decreased diuretic effect May increase serum digoxin concentrations Headache, visual hallucination, tremor, manic episodes May increase risk of bleeding Additive drug effects (herb may intensify side effects) Herb contains estrone, estradiol, estriol; Has additive estrogenic effects Ginseng may reduce the effectiveness of opioids
Goldenseal *(Hydrastis canadensis*)	Mucosal inflammation, gastritis	Anticoagulants	Contains berberine; inhibits anticoagulant effects & may increase risk of blood clots
Gossypol	Male contraceptive	Diuretics NSAIDs	Potentiate hypokalemia Increased gastrointestinal irritation
Guarana (*Paullinia cupana)*	CNS stimulant, potentiate analgesics	Anticoagulants	Inhibits platelet aggregation, increases risk of bleeding

HERB	COMMON INDICATION	DRUG	POTENTIAL EFFECT
Hawthorn (*Crataegus laevigata, C.monogyna, C.pinnatifida)*	Heart disease, sleep disorders angina	Antihypertensives Digoxin	High dose of herb causes hypotension Potentiates drug effect
Hops (*Humulus Lupulus L)*	Insomnia	Anxiolytics, alcohol	Potential additive sedation
Horse chestnut *(Aesculus hippocastanum)*	Varicose veins, other venous insufficiencies	Anticoagulants	Herb contains coumarin-like constituent; May increase risk of bleeding
Karela Bitter melon	Diabetes mellitus	Hypoglycemic drugs	Potentiates drug effect
Kava-Kava (*Piper methylsticum)*	Sleep disorders, anxiety	Alcohol, Benzodiazepines, CNS depressants	Additive sedative effects
Kelp *(Laminaria hyperborea)*	Thyroid dysfunction	Thyroid hormones	Herb contains iodine, may interfere with thyroid replacement
Kolanut Cola, Kola (*Cola nitida)*	Use in beverages for caffeine content	Theophylline, guarana caffeine	Herb contains caffeine, potential additive CNS stimulation
Lemon balm (*Melissa officinalis L)*	Insomnia, anxiety	CNS depressants Thyroid hormones	Potentiates CNS depression May bind thyrotropin and interferes with therapy

HERB	COMMON INDICATION	DRUG	POTENTIAL EFFECT
Licorice (*Glycyrrhiza glabra)*	Expectorant, peptic ulcers	Spironolactone	Antagonism of diuretic effect (increases production of aldosterone)
		Cardiac glycosides, Thiazide diuretics	Can cause hypokalemia; May potentiate digoxin toxicity
		Corticosteroids, Cyclosporine	Herb has immunostimulating effect; May decrease response to the drugs
		Antihypertensives	Can increase salt & water retention, making antihypertensives less effective
		Monoamine oxidase inhibitors	Herb contains sympathomimetic amines, increased risk of hypertensive crisis
Ma Huang Ephedra, squaw tea, mormon tea, popotillo, sea grape *(Ephedra species)*	Asthma, weight loss	Oxytocin, Methyldopa, B-blockers, Caffeine, Monoamine oxidase inhibitors, Theophylline, Sympathomimetics, St.John's wort, Guanethidine, Cardiac glycosides	Increased sympathomimetic action; may induce hypertension, CNS stimulation
Milk thistle *(Silybum marianum)*	Acute & chronic viral hepatitis, alcoholic hepatitis	Hypoglycemic drugs	May intensify the effects of these drugs, causing an excessive decrease in blood sugar levels
		Saquinavir	Decreases blood levels of saquinavir, making it less effective
Passionflower *(Passiflora incarnata)*	Anxiety, restlessness	Anticoagulants	Excessive dose may increase risk of bleeding
Pau D'Arco Taheebo, Trumpet bush *(Lapacho colorado)*	Antineoplastic	Anticoagulants	May potentiate drug effects

HERB	COMMON INDICATION	DRUG	POTENTIAL EFFECT
Psyllium Plantago, plantain *(Plantago species)*	Bulk-forming laxative, Irritable bowel syndrome, Cholesterol lowering	Lithium, digoxin Antihyperlipidemics Anticoagulants	Decreased intestinal drug absorption Possible additive effects Herb contains vitamin K; May interfere with anticoagulant therapy
Red clover *(Trifolium pratense)*		Anticoagulants	Herb contains coumarin; large amount may increase risk of bleeding
Sarsaparilla Honduras *(Smilax species)*	Diuretic	Digitalis, bismuth Drugs metabolized by CYP450 enzymes	Increased absorption of digitalis and bismuth Induces CYP450 enzymes; increases drug elimination
Saw palmetto Sabal, Cabbage palm *(Serenoa repens)*	Benign prostatic hyperplasia	Iron Estrogens	Tannin content of herb may limit iron absorption Potential additive effects
Senna *(Cassia acutifolia, C.augustifolia, Senna alexadrina)*	Constipation	Digitalis, Diuretics	Chronic use may cause hypokalemia and potentiate drug toxicity
Shankapulshpi (*Ayurvedic preparation)*		Phenytoin	Reduced drug concentrations and half-life; Decreased drug effect

HERB	COMMON INDICATION	DRUG	POTENTIAL EFFECT
Siberian ginseng *(Eleutherococcus, senticosus)*	Improve endurance	Digitalis	May interfere with drug level assay
St.John's wort *(Hypericum perforatum)*	Depression	Antidepressants (MAOI; SSRI), sympathomimetic amines, Ma Huang, pseudoephedrine, yohimbine	Herb may have monoamine oxidase inhibitor or selective serotonin reuptake inhibitor effects; Possible hypertensive crisis, serotonin syndromes
		Digoxin	Hypericum extract may reduce peak and trough digoxin concentrations
		Iron	Tannin content of herb may limit iron absorption
		Photosensitizers e.g. piroxicam, omeprazole, lansoprazole, sulfonamides	Increased risk of photosensitivity, avoid use with UV light therapy
		Indinavir	May reduce blood levels of indinavir making it less effective
		Cyclosporine	May reduce blood levels of cyclosporine making it less effective
		Warfarin	May reduce blood levels of warfarin making it less effective
		Benzodiazepines	May reduce the effectiveness of these drugs in reducing anxiety and may increase the risk of side effects such as drowsiness

HERB	COMMON INDICATION	DRUG	POTENTIAL EFFECT
Turmeric Tumeric, indian saffron *(Curcuma longa)*	Dyspepsia	Antiplatelet agents	Herb contains curcumin; may potentiate antiplatelet activity
Uzara root *(Uzarae radix)*	Diarrhea	Digoxin	Additive digoxin-like cardiac effects
Valerian *(Valeriana officinalis)*	Anxiolytics	Opiates, Alcohol, Barbiturates, CNS depressants	Additive sedation
Wormwood	Loss of appetite, dyspepsia	Anticonvulsants	May lower seizure threshold
Yohimbe Yohimbine *(Pausinystalia yohimbe)*	Impotence	Antihypertensives, Caffeine, Ephedrine, Ma Huang _____ Antidepressants, St. John's Wort	Herb has *α2*-antagonist activity My induce hypotension or hypertension, tachycardia. _____ May have monoamine oxidase inhibitor activity
Pycnogenol/ Grape seed	Anti-oxidant, Anti-inflammatory	Anticoagulants _____ Cholesterol lowering drugs	Excessive bleeding _____ Interferes with their action
Cranberry	Urinary tract infections, Acidifies urine		Cranberry juice has a moderately high concentration of oxalate, a common component of kidney stones, and should be limited in patients with a history of nephrolithiasis

Botanical Supplements And Some Associated Risks

Commercial Name, Scientific Name, Plant Parts	Intended Use	Toxic Agents. Effects	Comments
Comfrey **Symphytum** species Leaves and roots	Internal digestive aid, topical for wound healing	Pyrrolizidine alkaloids, hepatotoxicity	Avoid internal ingestion: topical use should be limited to 4-6 weeks
Coltsfoot *Tussilago farfara* Leaves, flower	Upper respiratory tract infections	Pyrrolizidine alkaloids, hepatotoxicity	Avoid ingestion of any parts of plant; leaves may be used topically for anti-inflammatory effects for up to 4-6 weeks
Germander *Teucrium chamaedrys* Leaves,tops	Diet aid	Hepatotoxicity	Avoid
Borage *Borago officinalis* Tops, leaves	Anti-inflammatory, diuretic	Pyrrolizidine alkaloids, hepatotoxicity	Avoid
Chaparral *Larrea tridentata* Twigs, leaves	Anti-infective, antioxidant, anticancer	Hepatotoxicity	Avoid
Sassafras *Sassafras albidum* Root bark	Blood thinner	Safrole oil, hepatocarcinogen in animals	Avoid
Aconite Aconitum species	Analgesic	Alkaloid, cardiac and central nervous system effects	Avoid
Pennyroyal Mentha pulegium or Hedeoma pulegioides Extract	Digestive aid, induction of menstrual flow, abortifacient	Pulegone and pulegone metabolite, liver failure, renal failure	Avoid

Commercial Name, Scientific Name, Plant Parts	Intended Use	Toxic Agents. Effects	Comments
Poke root *Phytolacca americana*	Anti rheumatic	Hemorrhagic gastritis	Avoid
Jin Bu Huan	Analgesic; sedative	Hepatotoxicity	Avoid
Ephedra, Ma huang Ephedra species	Diet aid; stimulant; bronchodilator	Central nervous system toxicity, cardiac toxicity	Avoid in patients at risk for stroke, myocardial infarction, uncontrolled blood pressure, seizures, general anxiety disorder
Royal jelly Apis mellifera (honeybee)	Tonic	Bronchospasm, anaphylaxis	Avoid in patients with chronic allergies or respiratory diseases; asthma, chronic obstructive pulmonary disease, emphysema, atopy

Food & Drug Interactions

- Medicines can treat and cure many health problems. However, they must be taken properly to ensure that they are safe and effective. Many medicines have powerful ingredients that interact with the human body in different ways, and diet and lifestyle can sometimes have a significant impact on a drug's ability to work in the body.

- Certain foods, beverages, alcohol, caffeine, and even cigarettes can interact with medicines. This may make them less effective or may cause dangerous side effects or other problems.

- Changes in a medicine's effect due to an interaction with food, alcohol or caffeine can be significant; however, there are many individual factors that influence the potential for such variations, like dose, age, weight, sex, and overall health.

This brochure has information about possible interactions between many medications with food, alcohol and caffeine. It is also important to remember that many drugs interact with other drugs and may cause serious medical conditions.

ALLERGIES

Antihistamines are used to relieve or prevent the symptoms of colds, hay fever, and allergies. They limit or block histamine, which is released by the body when a patient gets exposed to substances that cause allergic reactions. These products vary in their ability to cause drowsiness and sleepiness.

ANTIHISTAMINES

- Some examples are:

Brompheniramine, chlorpheniramine, diphenhydramine, fexofenadine, loratadine, cetirizine

- Interaction

1. Food: It is best to take antihistamines (especially second generation) on an empty stomach to increase their effectiveness.

2. Alcohol: Some antihistamines may increase drowsiness and slow mental and motor performance. Operating machinery or driving should be done cautiously.

ARTHRITIS AND PAIN

ANALGESIC / ANTIPYRETIC

They treat mild to moderate pain and fever.

- An example is: acetaminophen (paracetamol)
- Interactions

1. Food: For rapid pain relief, the drug can be taken on an empty stomach because food may slow the body's absorption of acetaminophen.

2. Alcohol: Avoid or limit the use of alcohol because chronic alcohol use can increase the risk of liver damage or stomach bleeding.

NON-STEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDS)

- NSAIDs reduce pain, fever, and inflammation.
- Some examples are: aspirin, ibuprofen, naproxen, ketoprofen.
- Interaction

1. Food: Because these medications can irritate the stomach, they are best taken with food or milk.

2. Alcohol: Avoid or limit the use of alcohol because chronic alcohol use can increase the risk of liver damage or stomach bleeding.

3. Buffered aspirin or enteric coated aspirin may be preferable to regular aspirin to decrease stomach bleeding.

CORTICOSTEROIDS

- They are used to provide relief to inflamed areas of the body. Corticosteroids reduce swelling and itching, and help relieve allergic, rheumatoid, and other conditions.

- Some examples are: methylprednisolone, prednisone, prednisolone

- Interaction

1. Food: Take with food or milk to decrease stomach upset.

NARCOTIC ANALGESICS

- Narcotic analgesics are available only with a prescription. They provide relief for moderate to severe pain. Codeine can also be used to suppress cough. Some of these medications can be found in combination with non-narcotic drugs such as cough syrups.

- These medications should be taken very cautiously because they may be habit forming and can cause serious side effects when used improperly.

- Some examples are: codeine, morphine, oxycodone, meperidine.

- Interaction

1. Alcohol: Avoid alcohol because it increases the sedative effects of the medications.

ASTHMA

BRONCHODILATORS

- Bronchodilators are used to treat the symptoms of bronchial asthma, chronic bronchitis and emphysema. These medicines open air passages to the lungs to relieve wheezing, shortness of breath and troubled breathing.

- Some examples are: theophylline, albuterol (salbutamol), epinephrine (adrenaline)

- Interactions

1. Food: The effect of food on theophylline medications can vary widely. High-fat meals may increase the amount of theophylline in the body, while high-carbohydrate meals may decrease it.

It is important to check with the pharmacist about which form is taken because food can have different effects depending on the dosage form (e.g., regular release, sustained release).

2. Caffeine: Avoid large amounts of foods and beverages that contain caffeine (e.g., chocolate, colas, coffee, tea) because both oral bronchodilators and caffeine stimulate the central nervous system.

3. Alcohol: Avoid alcohol with theophylline medications because it can increase the risk of side effects such as nausea, vomiting, headache and irritability.

CARDIOVASCULAR DISORDERS

- There are numerous medications used to treat cardiovascular disorders such as high blood pressure, angina, arrhythmias, and high cholesterol.

- These drugs are often used in combination to enhance their effectiveness. Some classes of drugs can treat several conditions.

For example, beta blockers can be used to treat high blood pressure, angina, and arrhythmias.

- Some of the major cardiovascular drug classes are:

DIURETICS

- Diuretics help eliminate water, sodium, and chloride from the body.

- There are different types of diuretics.

Some examples are: furosemide, hydrochlorothiazide, triamterene, triamterene + hydrochlorothiazide, bumetamide, metolazone.

- Interaction

1. Food: Diuretics vary in their interactions with food and specific nutrients.

a. Some diuretics cause loss of potassium, calcium, and magnesium e.g. furosemide.

b. Triamterene, on the other hand, is known as a "potassium-sparing" diuretic. It blocks the kidneys' excretion of potassium, which can cause hyperkalemia. Excess potassium may result in irregular heartbeat and heart palpitations. With triamterene, avoid large amounts of potassium-rich foods such as bananas, oranges and green leafy vegetables, or salt substitutes that contain potassium.

BETA BLOCKERS

- Beta blockers decrease the nerve impulses to the heart and blood vessels. This decreases the heart rate and the work load of the heart.

- Some examples are: atenolol, metoprolol, propranolol, nadolol.

- Interaction

1. Alcohol: Avoid alcohol with propranolol because the combination lowers blood pressure too much.

NITRATES

- Nitrates relax blood vessels and lower the demand for oxygen by the heart.
- Some examples are: isosorbide dinitrate, nitroglycerin.
- Interaction

1. Alcohol: Avoid alcohol because it may add to the blood vessel-relaxing effect of nitrates and result in dangerously low blood pressure.

ANGIOTENSIN CONVERTING ENZYME (ACE) INHIBITORS

- ACE inhibitors relax blood vessels by preventing angiotensin II, a vasoconstrictor, from being formed.

- Some examples are: captopril, enalapril, lisinopril

- Interactions

1. Food:

a. Food can decrease the absorption of captopril. So captopril should be taken one hour before or two hours after meals.

b. ACE inhibitors may increase the amount of potassium in the body. So avoid large amounts of foods high in potassium such as bananas, green-leafy vegetables, and oranges.

HMG-CoA REDUCTASE INHIBITORS

- Otherwise known as "statins," these medications are used to lower cholesterol. They work to reduce the rate of production of LDL cholesterol.
- Some of these drugs also lower triglycerides.
- Recent studies have shown that pravastatin can reduce the risk of heart attack, stroke, or miniature stroke in certain patients.
- Some examples are: atorvastatin, cerivastatin, fluvastatin, lovastatin, pravastatin, simvastatin.

- Interaction

1. Alcohol: Avoid drinking large amounts of alcohol because it may increase the risk of liver damage.

2. Food: Lovastatin should be taken with the meals to enhance absorption.

ANTICOAGULANTS

- Anticoagulants help to prevent the formation of blood clots.
- An example is: warfarin
- Interactions

1. Food:

a. Vitamin K reduces the effectiveness of anticoagulants. So limit the amount of foods high in vitamin K (such as broccoli, spinach, kale, turnip greens, cauliflower, and brussel sprouts).

b. High doses of vitamin E (400 IU or more) may prolong clotting time and increase the risk of bleeding.

INFECTIONS

ANTIBIOTICS AND ANTIFUNGALS

- Many different types of drugs are used to treat infections caused by bacteria and fungi.
- Some general advice for the patient when taking any such product is:

1. Consult the doctor about any skin rashes that might appear while taking antibiotics. A rash can be a symptom of an allergic reaction, and allergic reactions can be very serious.

2. Consult the doctor if diarrhea occurs.

3. If using birth control, consult the health care provider because some methods may not work when taken with antibiotics.

4. Finish all the medication even after feeling better.

5. Take with plenty of water.

ANTIBACTERIALS

PENICILLIN

- Some examples are: penicillin V, amoxicillin, ampicillin
- Interaction

1. Food: Taken on an empty stomach, but if it upsets the stomach, taken with food.

CEPHALOSPORINS

- Some examples are: cefaclor, cefadroxil, cefixime, cefprozil, cephalexin.

- Interaction

1. Food: Taken on an empty stomach one hour before or two hours after meals. If stomach gets upset ⟶ drug taken with food.

QUINOLONES

- Some examples are: ciprofloxacin, levofloxacin, ofloxacin, trovafloxacin.

- Interactions

Food:

1. Taken on an empty stomach one hour before or two hours after meals. If stomach gets upset, medication is taken with food.

2. Calcium-containing products like milk, yogurt, vitamins or minerals containing iron, and antacids should be avoided because they significantly decrease drug concentration.

3. Caffeine: Taking these medications with caffeine- containing products (e.g., coffee, colas, tea, and chocolate) may increase caffeine levels, leading to excitability and nervousness.

MACROLIDES

- Some examples are: azithromycin, clarithromycin, erythromycin erythromycin + sulfisoxazole (PEDIAZOLE)

- Interaction

1. Food: Taken on an empty stomach one hour before or two hours after meals. If stomach gets upset ⟶ drug taken with food.

SULFONAMIDES

- An example is: sulfamethoxazole + trimethoprim (BACTRIM)

- Interaction

1. Food: Taken on an empty stomach one hour before or two hours after meals. If stomach gets upset ⟶ drug taken with food.

TETRACYCLINES

- Some examples are: tetracycline, doxycycline, minocycline

- Interaction

1. Food:

a. Taken on an empty stomach one hour before or two hours after meals. If stomach gets upset ⟶ drug taken with food.

b. However, it is important to avoid taking tetracycline with dairy products, antacids and vitamins containing iron because these can interfere with the medication's effectiveness.

NITROIMIDAZOLE

- An example is: metronidazole (FLAGYL)
- Interaction

1. Alcohol:

Patient should avoid drinking alcohol or using medications that contain alcohol or eating foods prepared with alcohol while taking metronidazole and for at least three days after finishing the medication. Alcohol may cause nausea, abdominal cramps, vomiting, headaches, and flushing (disulfiram-like action of the drug).

ANTIFUNGALS

- Some examples are: fluconazole, griseofulvin, ketoconazole, itraconazole
- Interaction

1. Food:

a. These medications should not be administered with dairy products (milk, cheeses, yogurt, ice cream).

b. These medications should not be administered with antacids; since acidic medium is essential for the dissolution of these drugs.

2. Alcohol: patient should avoid drinking alcohol, using medications that contain alcohol, or eating foods prepared with alcohol while taking ketoconazole and for at least three days finishing the medication.

MOOD DISORDERS

Depression, Emotional, and Anxiety Disorders

- Depression, panic disorder and anxiety are a few examples of mood disorders — complex medical conditions with varying degrees of severity.
- When using medications to treat mood disorders it is important to instruct the patient to take the medication as directed even if he feels better. In some cases it may take several weeks for an improvement in symptoms to occur.

MONOAMINE OXIDASE (MAO) INHIBITORS

- Some examples are: phenelzine, tranylcypromine

- Interactions

1. MAO Inhibitors have many dietary restrictions, and people taking them need to follow the dietary guidelines and physician's instructions very carefully. A rapid, potentially fatal increase in blood pressure can occur if foods or alcoholic beverages containing tyramine are consumed while taking MAO Inhibitors.

2. Alcohol: should be avoided.

3. Food: Foods high in tyramine that should be avoided include:

1. Processed, cheddar, blue, brie, mozzarella and Parmesan cheese; yogurt, sour cream.

2. Beef or chicken liver; cured meats such as sausage and salami; caviar; dried fish.

3. Avocados, bananas, yeast extracts, raisins, sauerkraut, soy sauce, miso soup.

4. Broad (fava) beans, ginseng, caffeine-containing products (colas, chocolate, coffee and tea).

ANTI-ANXIETY DRUGS

- Some examples are: lorazepam, diazepam, alprazolam

- Interaction

1. Alcohol: May impair mental and motor performance (e.g., driving, operating machinery).

2. Caffeine: May cause excitability, nervousness, and hyperactivity and lessen the anti-anxiety effects of the drugs.

ANTIDEPRESSANT DRUGS

- Some examples are: paroxetine, sertraline, fluoxetine.
- Interactions

1. Alcohol: Although alcohol may not significantly interact with these drugs to affect mental or motor skills, people who are depressed should not drink alcohol.

2. Food: These medications can be taken with or without food.

STOMACH CONDITIONS

Conditions like acid reflux, heartburn, acid indigestion, sour stomach, and gas are very common ailments. The goal of treatment is to relieve pain, promote healing and prevent the irritation from returning. This is achieved by either reducing the acid the body creates or protecting the stomach from the acid. Lifestyle and dietary habits can play a large role in the symptoms of these conditions. For example, smoking cigarettes and consuming products that contain caffeine may make symptoms return.

HISTAMINE BLOCKERS

- Some examples are: cimetidine, famotidine, ranitidine, nizatadine.

- Interactions

1. Alcohol: Avoid alcohol while taking these products. Alcohol may irritate the stomach and make it more difficult for the stomach to heal.

2. Food: Can be taken with or without regard to meals.

3. Caffeine: Caffeine products (e.g., cola, chocolate, tea and coffee) may irritate the stomach.

Grape Fruit Juice & Drugs

Is there a role for grape fruit juice in therapeutics?

- This is a very interesting question. In the USA there are anecdotal reports of patients being counseled to take their medications with grapefruit juice (GJ) to boost the blood levels of the medication.
- While this may be appropriate in specific clinical situations, health care professionals should not routinely counsel patients to use GJ to increase the blood levels and effects of their medication.
- The most reasonable guideline for health care professionals to follow is to counsel patients that if they are not currently taking their medications with GJ regularly, don't start. If they are already taking their medications with GJ regularly, don't stop.
- If this interaction is to ever be used therapeutically, it could be with drugs that undergo complete first-pass metabolism, and are therefore only active by the intravenous route. Also, drug which undergo incomplete first-pass metabolism could be co-administered with GJ to produce more consistent bioavailability and clinical response.
- It is advisable not to consume grapefruit or grapefruit juice while taking medications used to treat anxiety, depression, high blood pressure, HIV/AIDS, cancer, irregular heart rhythms, infections, psychotic problems, erectile dysfunction, angina, convulsions, gastrointestinal reflux, high cholesterol, or organ graft rejections due to the risk of potentially serious interference with blood drug levels.

Basic Mechanism of Action

Drugs that interact with grapefruit juice (GJ) undergo cytochrome p450 oxidative metabolism in the intestinal wall or liver. GJ contains various bioflavonoids which have been demonstrated to affect the cytochrome p450(CYP) system (especially at isoenzymes CYP1A2, and CYP3A4) by binding to the isoenzyme as a substrate and impairing first-pass metabolism, either by direct inactivation or inhibition of the enzyme.

The net effect on the CYP enzymes from this inhibition seems to be a selective down-regulation of CYP3A4 in the small intestine.

Naringin

Naringin is the main bioflavonoid in GJ. Naringin is not a potent CYP inhibitor, but is partially metabolized by enteral bacteria to naringenin, which is a potent inhibitor of p450 enzymes, and was originally thought to be the component of GJ responsible for the interactions, although it was thought possible that another unidentified component in grapefruit may also have been responsible, since giving naringin alone does not seem to cause the same degree of inhibition as GJ.

Furanocoumarins/Bergamottin

- Researchers have isolated a group of compounds from GJ called furanocoumarins, which appear to be specific CYP3A4 inhibitors.
- Further *in vito* studies determined that several compounds found in GJ inhibit CYP3A4 enzymes. Specifically, these were nootkanone (a sesquiterpene), and 4 derivatives of coumarin, geranyloxycoumarin, bergamottin, and 2 chemical with very long technical names, denoted as GF-I-1 and 4.

- Results of confirmatory *in vivo* testing of CYP3A4 inhibition with externally administered GF-I-1 and GF-I-4 have shown that wide inter-individual variability in response to these interactions is present.

P-glycoprotein

- Studies on GJ have revealed that it significantly activates p-glycoprotein mediated reduction in bioavailability, partially counteracting the CYP3A4 inhibitory effects of GJ. This may explain why the effect of GJ on drug absorption is unpredictable and highly variable.
- P-glycoprotein is an efflux pump that, like CYP3A enzymes, is located at high levels in intestinal enterocytes, the primary site of oral absorption, where it actively secretes absorbed drug back into the gut lumen.
- Drugs studied included vinblastine, cyclosporine, digoxin (Lanoxin), fexofenadine (Allegra) and losartan (Cozaar) (as CYP3A and/or p-glycoprotein substrates) as well as felodipine (Plendil, Renedil) and nifedipine (Adalat, Procardia) (primarily CYP3A substrates):
    1. The efflux of vinblastine, cyclosporine, digoxin, fexofenadine and losartan were increased in the presence of GJ, while no increased efflux of nifedipine and felodipine was noticed when GJ was added.
    2. It should be emphasized that this experiment was performed in laboratory cell cultures, and is not a human trial, but it does point the way for further studies on p-glycoprotein effects observed in this study.

3. The actual effects of GJ on absorption of drugs not studied in humans (vinblastine (not given orally), digoxin, fexofenadine and losartan) are unknown.

Confirmation of effect of raw grapefruit and extract

- Studies confirmed that the activity of grapefruit segments and an extract of the peel and rind had similar drug interaction potential to the juice.
- It was concluded if there is a concern for a drug interaction with GJ, it seems logical to avoid consumption of grapefruit segments as well during pharmacotherapy with the affected drug(s).
- Confectioneries, like marmalades, made from grapefruit peel may also cause a drug interaction

Examples of Drugs Interacting with GJ

GJ drug interactions (DIs) with non-sedating antihistamines:

*** *Desloratadine* (Clarinex)**

Desloratidine does not undergo primary metabolism via CYP 3A4, and is not a p-glycoprotein substrate, ∴GJ intake produces no changes in QTc intervals on the ECG & does not affect the rate or extent of desloratidine absorption.

*** *Fexofenadine* (Allegra)**

Bioavailability and peak serum concentration were decreased while no changes in QTc intervals on the ECG were noted in any patient receiving fexofenadine and GJ. This is unexpected since fexofenadine does not undergo significant biotransformation by CYP enzymes. However, co-administration of fexofenadine with ketoconazole and erythromycin, which as known CYP 3A4 inhibitors, resulted in significant increases in the extent of absorption of fexofenadine. (Ketoconazole and erythromycin have since been shown to inhibit p-glycoprotein).

This built on a study, which suggested that fexofenadine may be a substrate for organic anion transporting polypeptide (OATP), another transporter system, and that grapefruit, and possibly orange, apple, and grape juices may also affect disposition of fexofenadine through effects on OATP.

This study provided support for a new model of food-drug interaction, that includes the role of OATP, as well as CYP 3A4, and p-glycoprotein.

GJ drug interactions (DIs) with anti-infectives:

*** *Albendazole* (Albenza)**

Albendazole is an anthelminthic drug used for the treatment of intestinal parasites (eg. ascaris). Albendazole has poor absorption but this can be increased by taking the medication with a fatty meal. Albendazole is rapidly converted to its active metabolite albendazole sulfoxide, by CYP 3A4 enzymes in the intestine and liver.

GJ causes an increase in peak serum concentration & in bioavailability of albendazole.

Albendazole half-life is decreased & time to peak concentration is prolonged by GJ, an unexpected finding.

**** Praziquantel***

Praziquantel has a generally low and variable bioavailability. GJ increases the bioavailability & peak serum concentration of the drug while elimination half-life and time to peak level are not significantly affected. The joint administration of praziquantel and GJ could lead to a further improvement in the effectiveness of praziquantel therapy.

*** *Clarithromycin* (Biaxin)**

Administration of GJ increases the time to peak concentration of clarithromycin and its 14-hydroxy metabolite, but does not otherwise affect pharmacokinetic parameters.

Clarithromycin can safely be consumed with GJ without concern that the drugs antimicrobial activity may be altered, due to a pharmacokinetic interaction.

*** *Erythromycin* (Erythrocin)**

GJ slightly increases the bioavailability & peak serum concentration of erythromycin, but not to a beneficial level, since high antibiotic levels are

desired for treatment of susceptible infections. Half-life and time to peak concentration are not affected.

**** Indinavir* (Crixivan)**

Peak serum concentration & bioavailability of the drug are decreased by GJ. Time to peak blood level is increased. However, concomitant administration of GJ with indinavir in HIV-infected subjects is not associated with uniform changes in indinavir bioavailability.

**** Saquinavir***

GJ increases the bioavailability & the peak serum concentration of the drug.

Some studies concluded that for most patients, ingestion of saquinavir with GJ results in an increase in drug exposure similar to that expected after doubling the dose.

The *in vivo* effects of grapefruit juice co-administration are most likely the result of effects of CYP 3A4 (inhibition and down regulation) and only to a minor extent on modulation of P-glycoprotein function.

In contrast to saquinavir, there is a decrease in the bioavailability of indinavir occuring with the concurrent administration of GJ. The effects of GJ on the disposition of ritonavir have not been reported.

Physicians should be aware of the difference in interactions between GJ, saquinavir and indinavir.

**** Itraconazole* (Sporanox)**

Itraconazole is an antifungal agent, often used for treatment of fungal infections resistant to other drugs, such as ketoconazole and fluconazole.

GJ has no significant effect on any pharmacokinetic parameter of itraconazole. Interestingly, orange juice significantly decreases half-life and bioavailability of itraconazole.

GJ drug interactions (DIs) with benzodiazepines:

*** *Alprazolam* (Xanax)**

GJ does not significantly increase the drug bioavailability and the peak serum concentration. Alprazolam has a high oral bioavailability, which suggests that it has a lower rate of first-pass metabolism, in contrast to triazolam. This explains the greater sensitivity to GJ interaction for triazolam. This suggests that an interaction between GJ and alprazolam does not need to be considered in the clinical situation.

*** *Diazepam* (Valium)**

GJ increases the bioavailability & the peak serum concentration of diazepam. It also postpones the time to reach peak concentration of diazepam.

*** *Triazolam***

GJ increases the bioavailability & the peak concentration of triazolam. Drowsiness therefore could be increased when triazolam is given concurrently with GJ.

This could have resulted from inhibition of triazolam metabolism during the elimination phase due to inhibition of hepatic CYP 3A4 activity.

The importance of these interactions is evident in patients with other conditions that might increase benzodiazepine bioavailability (e.g. advanced age, liver cirrhosis, concurrent use of other medications that inhibit cytochrome P450). These patients should be observed for increased sedation.

N.B. Physicians may consider counselling selected patients to avoid concurrent consumption of triazolam or diazepam and GJ. Injectable midazolam, will not be affected by GJ. Evidence now indicates alprazolam is safe with GJ.

GJ drug interactions (DIs) with calcium-channel blockers (CCBs):

**** Amlodipine (Norvasc), felodipine (Plendil), nifedipine (Adalat)***

The grapefruit juice-drug interaction seems to affect mainly the dihydropyridine family of calcium-channel blockers.

Tachycardia and decreased diastolic blood pressure were noted when felodipine was given with GJ hypertensive patients. GJ increases the bioavailability & hence the side effects (facial flushing, headache, dizziness) of felodipine. Grapefruit segments and an extract of the peel and rind also increase the drug's bioavailability

GJ increases the bioavailability of nifedipine & amlodipine.

It seems logical to avoid consumption of grapefruit during pharmacotherapy with the affected drug(s).

A clinical case report described GJ intake resulting in marked hypotension in a patient with renovascular hypertension taking large doses of nifedipine for blood pressure control.

**** Diltiazem* (Cardizem)**

Bioavailability & peak serum concentration of diltiazem are not affected by GJ.

**** Nimodipine* (Nimotop)**

GJ increases the bioavailability & the peak serum concentration of the drug. It also prolongs the time to peak concentration. Since GJ intake may contribute to the variability of nimodipine pharmacokinetics, the interaction should be avoided.

**** Nitredipine***

There is a marked inter-individual variability in the magnitude of the interaction.

**** Verapamil* (Isoptin)**

GJ has no significant effect on verapamil pharmacokinetic parameters.

N.B.

1) In most studies, the interactions were tested in healthy subjects. This is an important distinction, as patients with hypertension or other cardiac conditions may experience more pronounced effects on heart rate and blood pressure.

2) GJ can cause substantial increases in bioavailability of certain calcium-channel blockers, primarily the dihydropyridine type. Patients receiving these medications and drinking grapefruit juice regularly should be monitored for increased response. A reasonable guideline for health care professionals is to tell patients that if they are not currently taking their antihypertensive medications with grapefruit juice regularly, don't start. If they are already taking their medications with grapefruit juice regularly, and are not experiencing adverse effects, don't stop.

GJ drug interactions (DIs) with cholesterol-lowering drugs:

HMG-CoA Reductase Inhibitors ("-Statins")

**** Lovastatin* (Mevacor)**

GJ increases the peak concentrations & the bioavailability of lovastatin, it does not affect the half-life. It is advisable not to co-administer lovastatin with grapefruit.

**** Simvastatin* (Zocor)**

GJ increases the bioavailability, the peak serum concentration & the time to peak concentration of simvastatin. It is recommend that concomitant

use of grapefruit juice and simvastatin should be avoided, or the dosage of simvastatin should be greatly reduced.

**** Atorvastatin* (Lipitor)**

GJ increases the bioavailability of atorvastatin. It does not affect the peak concentration, but increases the time to peak concentration and half-life. Atorvastatin has two active metabolites: atorvastatin lactone and 2-hydroxyatorvastatin acid which are also affected by GJ. Atorvastatin kinetics are affected to a considerably smaller degree with lovastatin and simvastatin.

It is advisable that grapefruit juice, at least in large amounts, should not be used concomitantly with atorvastatin, or the dosage of atorvastatin should be reduced accordingly.

**** Pravastatin* (Pravachol)**

GJ has no significant effects on the pharmacokinetics of pravastatin, other than the time to peak concentration of the drug which is significantly prolonged with co-administration of GJ. Pravastatin is hydrophilic with an oral bioavailability of approximately 20%, and is excreted to a significant extent unchanged in the urine. CYP3A4 plays only a minor role in the metabolism of pravastatin, which explains why pravastatin is not susceptible to interaction with GJ and other CYP3A4 inhibitors.

**** Fluvastatin* (Lescol)**

There are no significant interactions between GJ and fluvastatin. Fluvastatin is predominantly metabolized by CYP2C9. It is not metabolized to a significant extent by other cytochrome subclasses, including CYP3A4. However, since fluvastatin demonstrates a moderate affinity for the CYP 3A4 isoenzyme, drugs or agents such as GJ that inhibit this enzyme...may represent a potential, at least in some patients, for drug interactions when combined with fluvastatin.

GJ drug interactions (DIs) with psychiatric medications:

*** *Buspirone* (BuSpar)**

GJ increases the bioavailability & the peak serum concentration of the drug. It also leads to the prolongation of the time to peak concentration & an increase in the drug's half-life. More incidence of side effects (including dizziness, nausea, drowsiness and tingling) could occur with co-administration of GJ.

Although buspirone has a relatively wide therapeutic index, concomitant use of at least large amounts of grapefruit juice with buspirone should be avoided.

*** *Carbamazepine* (Tegretol)**

Bioavailability of carbamazepine increases with GJ, the peak and trough carbamazepine concentrations also increase. Clinicians should instruct patients receiving carbamazepine to avoid consumption of grapefruits to avoid undue adverse effects. Carbamazepine has a narrow therapeutic index, and if toxicity is suspected or confirmed by serum level monitoring, the patient should be questioned about GJ intake.

*** *Clomipramine* (Anafranil)**

Clomipramine serum levels increase when taken concurrently with GJ. The magnitude of this increase may be sufficient to increase the risk of adverse effects in some patients.

*** *Clozapine* (Clozaril)**

Clozapine is an atypical antipsychotic drug, which is known to be metabolized via CYP 1A2 and CYP 3A4, to two principal metabolites, desmethylclozapine, and clozapine-N-oxide. GJ does not affect the bioavailability or the peak serum concentration of either clozapine, or its metabolites. GJ does not alter multiple-dose pharmacokinetics and pharmacodynamics of clozapine. One reason is that

enzymes other than CYP 3A4 (such as CYP 1A2 and CYP 2C19) mediate clozapine disposition.

**** Haloperidol*** **(Haldol)**

No interaction between the drug & GJ, this may be due to the weak specificity of CYP3A4 as a substrate and the relatively high bioavailability of haloperidol. GJ is probably safe for patients treated with haloperidol.

GJ drug interactions (DIs) with immunosuppressant:

Bioavailability & peak serum concentration increase when cyclosporine (Sandimmune) is given with GJ.

Adverse effects experienced by subjects receiving the drug with GJ were not reported. GJ may be a potentially useful agent to increase cyclosporine levels.

However, transplant patients shouldn't drink GJ while taking cyclosporine, unless specifically advised to do so by their transplant physician. If an interaction causing toxicity is suspected, monitoring of cyclosporine trough levels is recommended.

Concerning the interaction between GJ and tacrolimus, an immunosuppressant with similar function and metabolic pathways (CYP 3A4) to cyclosporine, patients may experience increases in trough level of the drug. Since increased adverse effects correlate with increased trough levels, the combination of tacrolimus and GJ should be used with caution.

Sirolimus (Rapamune) is metabolized extensively via CYP3A4 in the gut wall and liver, and may potentially have interactions with GJ, but this potential has not been scientifically studied.

A summary of some Names of medicinal herbs in Arabic, Latin & English

No	English Name	Latin Name	Name in Arabic
1	Alfalfa	Medicago sativa	الفا الفا صفصفة برسيم حجازي فصة
2	Aloe	Aloe vera	صبار- صبير –مقر –سولع مخزني
3	Angelica	Angelica archangelica	حشيشة الملاك
4	bearberry uva ursi	Arctostaphylo S uva ursi	عنب الديب – قلطب زحاف – بقس الصغير – عنب ديب - عيسران
5	Black cohosh	B aneberry Bugwort Squawroot Rattleroot Cimicifuga racemosa	اقني – عنقودية – قاتل البق
6	Borage	Borago officinalis	لسان الثور – حمحم مخزني – ابو الريش - كحلاء
7	Capsicum	C.fructescens - C.annum	فلفل شطة – فليفلة – فليفلة حمراء –فلفل حريف – فليفلة حادة – فلف رومي
8	Cascara	Rhanmus purshiana . Cascara sagrada	عوسج فارس – قلف مقدس – عجرم- نبق بورشيانا (كسكارا) لحاء نوع من انواع اشجار النبق
9	Chamomile	Matricaria recutita	البابونج الالماني – فراخ ام علي
10	Chaste berry	Vitex agnus -castus	كف مريم – حشيشة ابة شيح – شجرة الرهبان – كف الجزماء – شجرة ابراهيم – مدعى الحمام – ارثد – سرساد - منجكشت
11	Echinacea	Echinacea sp.	الاخنيسية
12	Evening Primerose	Oenothera biennis	زهرة الربيع المسائية – اخدرية – حشيشة الحمار
13	fever few	Tanacetum chrysanthemum	غرديب – كافورية – حشيشة الحمي
14	Ginger	Zingiber officinale	زنجبيل
15	Garlic	Allium sativum	ثوم – فوم

16	Ginkgo	Ginkgo biloba	الشفتين – شجر معابد- جنكة – جينكو - معبلة
17	Ginseng	Panax ginseng P .quiquefolium	الجنسنج الكورى او الصيني – رن شن – جذر الانسان – ارااليا – الجنسنج الامريكي – كسي يانع شن – جذر انسان
18	Golden seal	Hydrastis canadensis	حوذان مر – خاتم ذهب - هيدراستوس
19	Guarana	Paullinia cup ana	جوارانا
20	Hawthorn	Crataegus monogyna	الزعرور – الشوكة البيضاء – زعرور الادوية
21	Hops /bine	Humulus lupulus	جنجل – حشيشة الدينار – كرمة الشمال
22	Horse chestnut	Aesculus hippocastanum	الكستناء الهندي – قسطلة الحصان – ابو فروة – كستناء الجبل – قندلي – قسطل هندي
23	Kava kava	Piper methysticum	فلفل كاوا – فلفل مسكي – فلف مسكر – كاوا كاوا
24	Colanut	Cola nitida	كولا – جوز الزلج – جوز السودان
25	Lemon balm	Mellissa officinalis L	المليسة – الحبق الترجاني – ترجان – شاي فرنسة – مليسة ترنجان – بقلة ضب – حشيشة نحل – الحبق القرنفلي – حبق بربري – باذرنجوية
26	Liquorice	Glycyrrhiza glabra	سوس مجزني – عرقسوس – رب السوس
27	Ma Haung Ephedra	Ephedra alata Ephedra distachya Ephedra sinica	ذيل ماعز – علد – ايفيدرة – عنب بحر –علندة – عاذر – جاشية – عدام – عب البحر – عقد مزدوج السنابل – ايفيدرا – جاشية – عدام – العاذر – علندة – ماهوانغ
28	Milk thistle	Silybum marianum	حرشيف بري – شوك الجمل – لحلاح – خرفيش الجمال – عكوب – شكوك الدمن
29	Passion flower	Passiflora incarnata	زهرة الالام – زهرة الاحزان – زهرة الساعة – الامية ارجوانية
30	Psyllium Plantago	P.ovata P.psyllium P.s£p.	زباد – كنباثي – لقمة نعجة – نبات بيضي – ودنة – انم – مصيص – بزر قطونة – عسبة البراغيث – اذنية حمل – قطنية – خزام ربل
31	Red clover	Trifolium pratense	نفل المروج – نفل بنفسجي
32	Rough bindweed Sarsaparilla Honduras	Smilax aspera -S.bona-nox S.china	فشاع قاس – عشبة مغربية – عشبة المغرب – فشاغ – العشبة – سار ساباريل – فشاغ صيني – عشبة – فشاع زراعي
33	Saw Palmetto	Serenoa serrulata	البلميط المنشاري – نخل قصير

34	Senna	C.acutifolia C.angustifolia C.senna	سنامكي – سلامكي – سنة ملكي – السنا هندي – سنا امريكي السنا – قسا - مريلاند
35	St. John's wart	Hypericum perforatum	حشيشة الكبد – حشيشة القلب- هيوفاريقون – داذي رومي –منسية – عشبة لسع – عشبة شياطين
36	tumeric curcuma	Curcuma longa	اصابع صفر – كركرم – زعفران الهند – مايران - هرد
37	Cat's valerian	valeriana officinalis	النرددبن الطبي – سنبل – حشيشة القط – ناريدن مخزني
38	yohim be/yohimbine	Pausinystalia yohimbe	يوهيمبين
39	Comfrey	Symphytum sp.	سنفتيون
40	coItsfoot cough wort	Tussilago farfara	حشيشة السعال – فرفارة – طارد سعال – طفوف كرمة – دوسة الحمار
41	Gennander,groud oak	Teucrium chamaedrys	جعدة – كمادريوس – طوقريونمخزني - خمادريوس
42	Chaparral	Larrea divaricata	دغل اجمة
43	Sassafras	Sassafras albidum	السافراس – نبات امريكي من الفصيلة العازية
44	Aconite Monkes hood wolfs bane Blue rocket,friar's cap.	Aconitum napellus	بيش موش – خانق الذئب – قاتل النمر – اقونيط – كونيطن – بيش البير – اكونيت هرمي – بيشا – طوارة – بيس حدس
45	Pennyroyal	Mentha pulegium Hedeoma pulegioides	نعناع الماء –فوذنج فلية – فليحا – نعنع الحقل – نعناع الماء الامريكي
46	Poke	Phytolacca americana	عنب الذئب
47	Royal jelly	Apis mellifera (honey bee	غذاء ملكات النحل

Some Herbs were not found in references:

*** Bromelain**
*** Dong Quai**
*** Gossypol**
*** Karela**
*** Kelp**
*** Pall** D' **Areo**
*** Shankapulsshpi**
*** Siberian ginseng**
* U **zara root**
*** Worm wood**
*** Pyehnogenol**
*** Cranberry**
*** Jin Bu Huan**

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