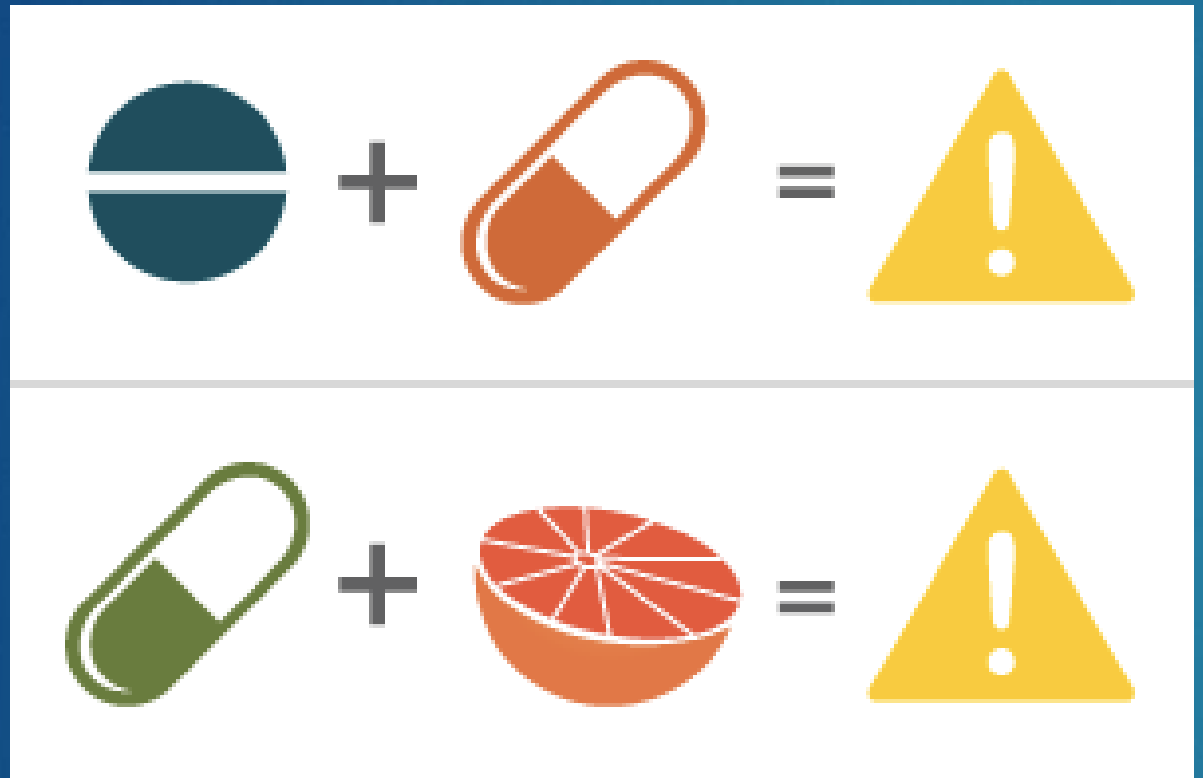
Drug Interactions



Outline

- Introduction
- Pharmacokinetic interactions
- Pharmacodynamic interactions
- Important drug interactions
- Interactions of herbal medications
- How to interpret drug interactions

Introduction

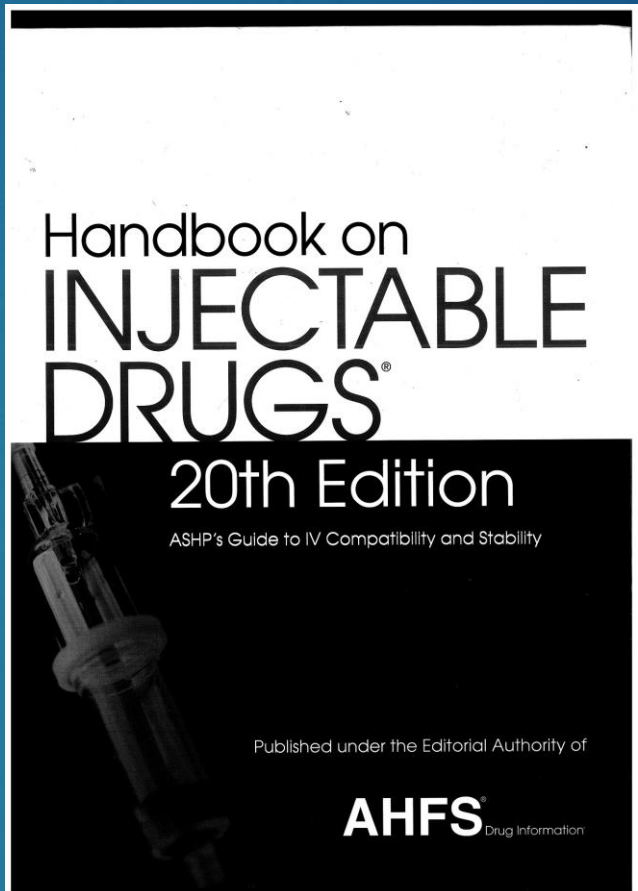
- Drug interactions occur when **one drug modifies the actions of another drug in the body.**

- Drug interactions can **result from**
  - **Pharmacokinetic alterations**
  - **Pharmacodynamic changes**
  - **Combination of both**

Introduction

- ***Drug incompatibilities***
  - Interactions between drugs **in vitro** (e.g., precipitation when mixed in solutions for intravenous administration)

Not drug interactions



Introduction

- Although **thousands** of drug interactions have been **documented**, relatively **few** are of enough clinical significance to constitute a **contraindication** to simultaneous use or to **require a change in dosage**.

- In patients taking many drugs, however, the likelihood of significant **drug interactions is increased**.

Introduction

- **Elderly** patients have a **high incidence** of drug interactions because they often have
  - **Age related changes in drug clearance**
  - **Commonly take multiple medications**

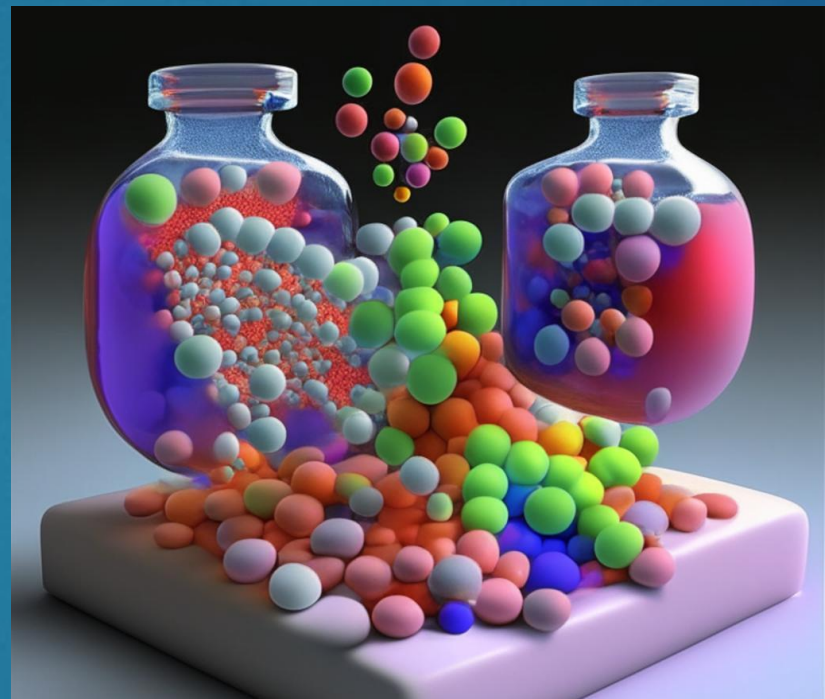
PHARMACOKINETIC INTERACTIONS

Interactions Based on Absorption

- **Absorption** from the **gastrointestinal tract** may be **influenced** by
  - **Agents that bind drugs (e.g., resins, antacids, calcium-containing foods)**
  - **Agents that increase or decrease gastrointestinal motility (e.g., metoclopramide or antimuscarinics, respectively)**
  - **Drugs that alter the P-glycoprotein and organic anion transporters in the intestine**

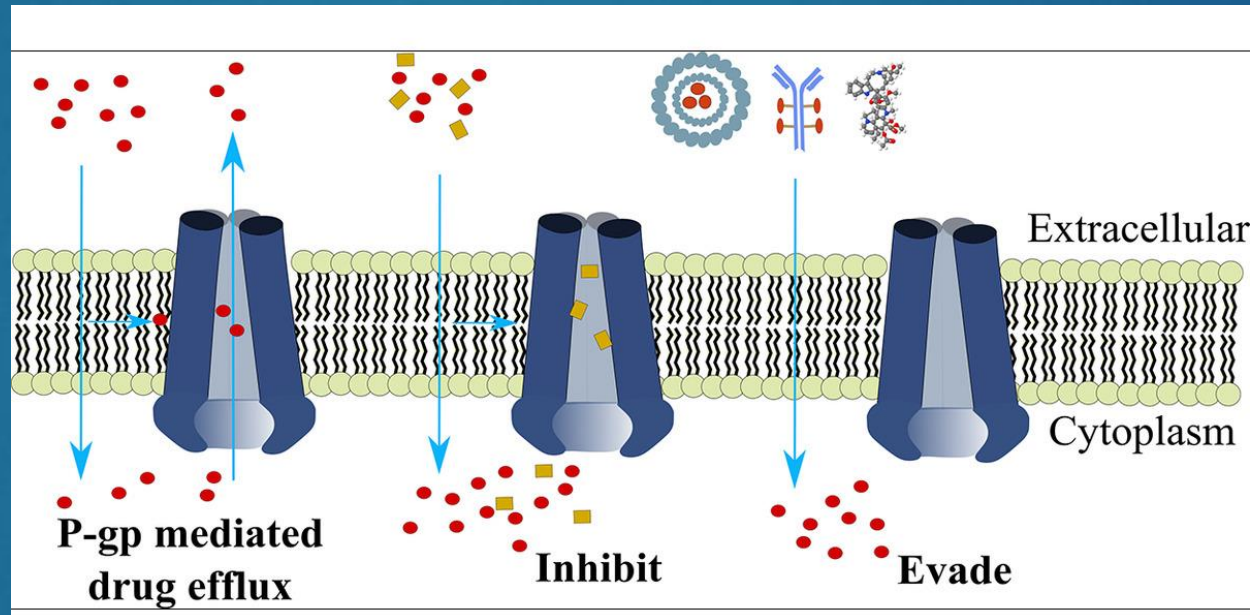
Interactions Based on Absorption

- Concomitant use of **antacids**, which **increase gastric pH**, can **decrease gastrointestinal absorption** of
  - **Digoxin**
  - **Ketoconazole**
  - **Quinolone antibiotics**
  - **Tetracyclines**



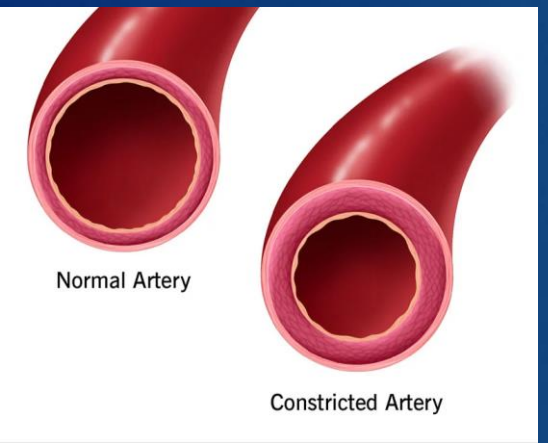
Interactions Based on Absorption

- Compounds in **grapefruit juice** and **some drugs** **inhibit** the **P-glycoprotein drug transporter** **in the intestinal epithelium and may increase the net absorption of drugs that are normally expelled by the transporter.**



Interactions Based on Absorption

- Absorption from subcutaneous sites can be **slowed** predictably by
  - **Vasoconstrictors** given simultaneously (e.g. **local anesthetics and epinephrine**)
  - Cardiac depressants that decrease tissue perfusion (e.g., β blockers)

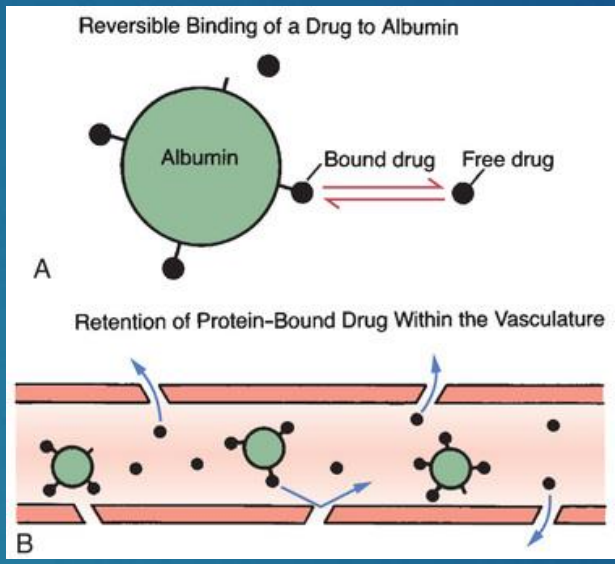


Interactions Based on Distribution and Binding

Interactions Based on Distribution and Binding

- Distribution of a drug can be **altered** by **other drugs that compete for binding sites on plasma proteins**
- Antibacterial sulfonamides can displace
  - Methotrexate
  - Phenytoin
  - Sulfonylureas
  - Warfarin

  } Binding sites on albumin

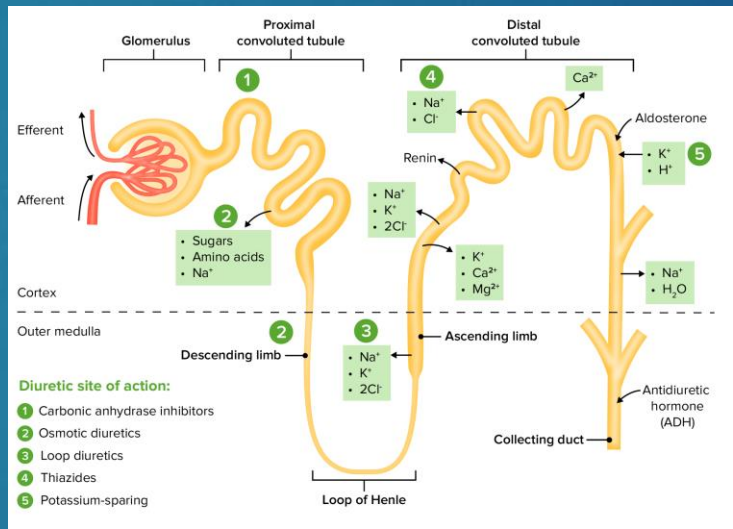


- However, it is difficult to document many clinically significant interactions of this type, and they seem to be the exception rather than the rule.

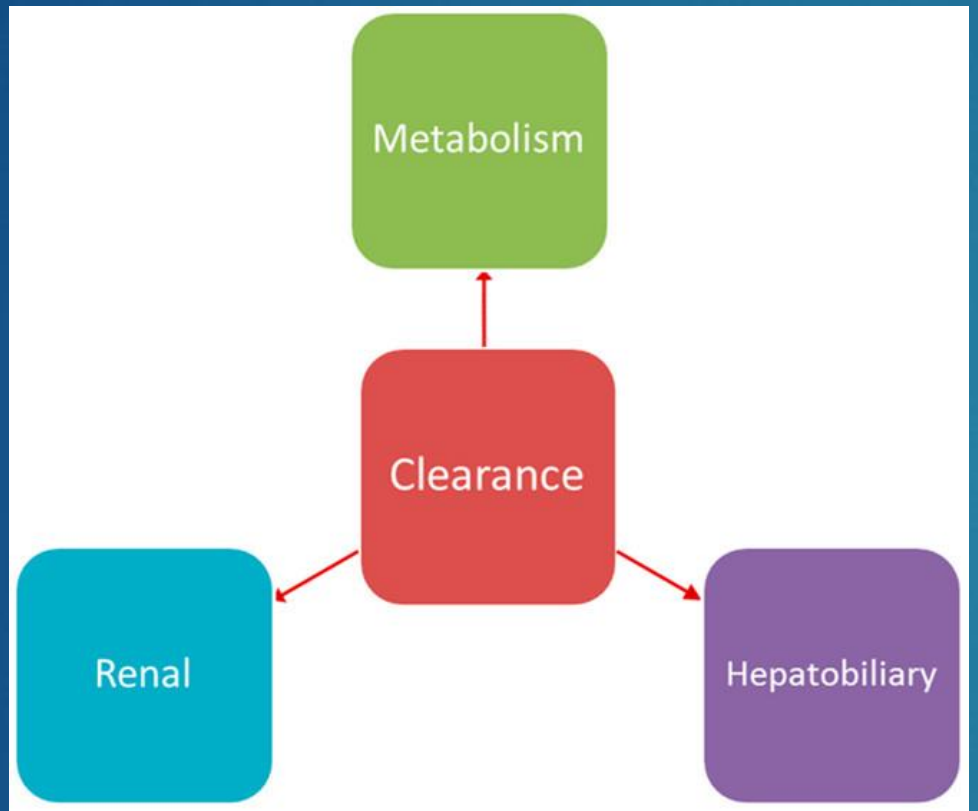
Interactions Based on Distribution and Binding

- **Changes in drug distribution** can occur if **one agent alters the size of the physical compartment in which another drug distributes.**

- For example, **diuretics**, by **reducing total body water**, can **increase plasma levels of aminoglycosides and lithium, possibly enhancing drug toxicities.**

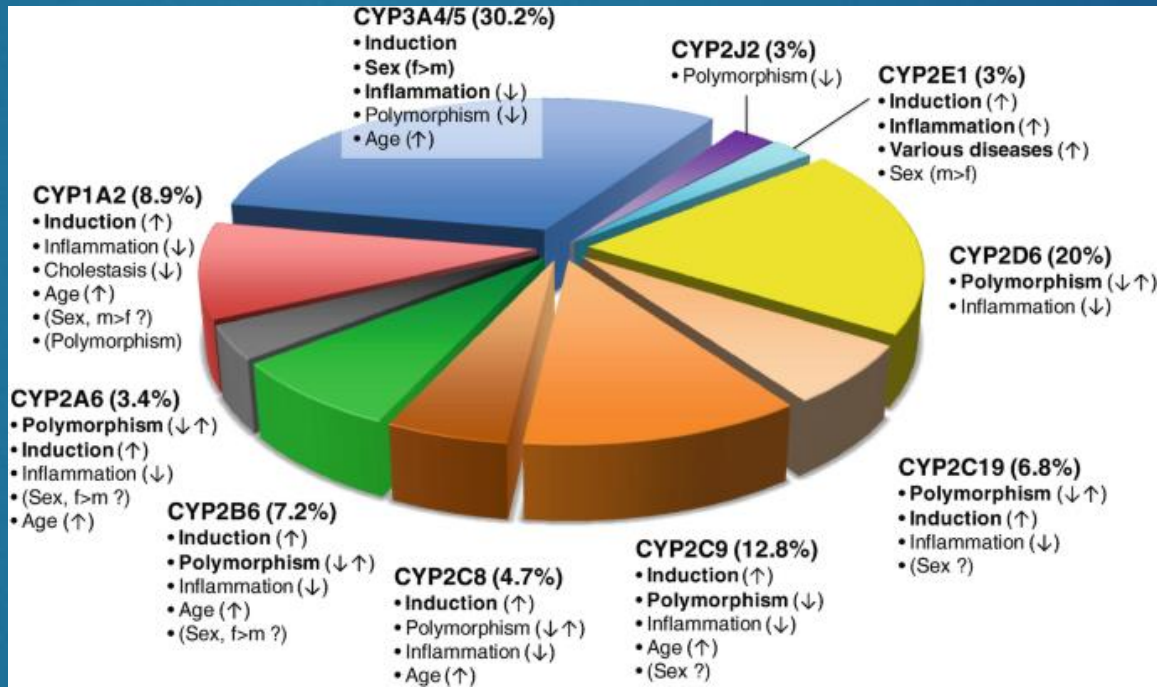


Interactions Based on Metabolic Clearance



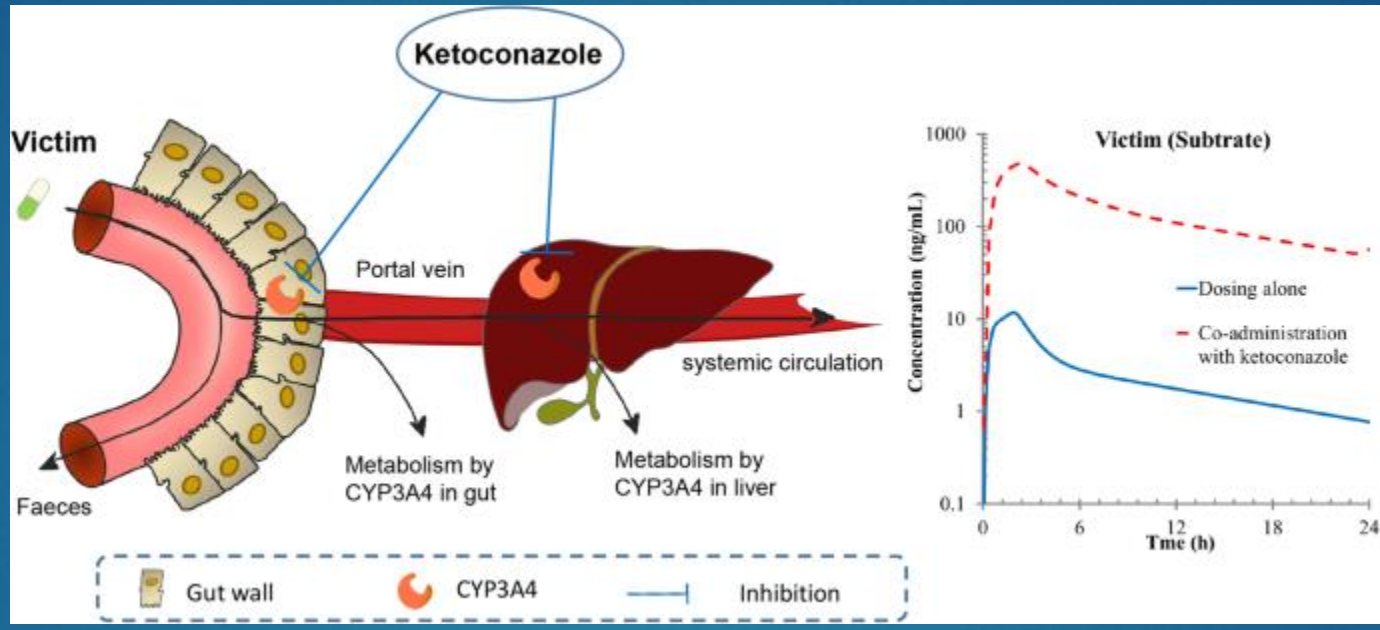
Interactions Based on Metabolic Clearance

- Drug interactions of this type are well documented and have considerable clinical significance.
- The metabolism of many drugs can be **increased** by other agents that **induce hepatic drug-metabolizing enzymes**, especially **cytochrome P450 isozymes**.
- **Induction** of drug metabolizing enzymes occurs predictably with chronic administration of
  - **Barbiturates**
  - **Carbamazepine**
  - **Ethanol**
  - **Phenytoin**
  - **Rifampin**



Interactions Based on Metabolic Clearance

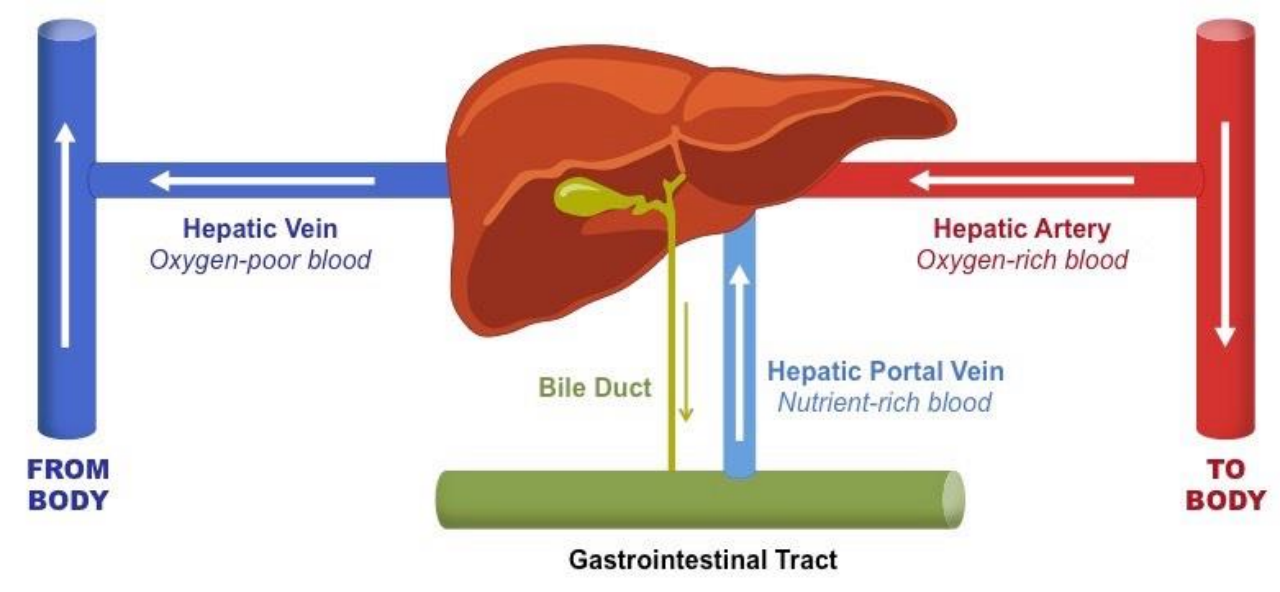
- Conversely, the metabolism of some drugs may be **decreased** by other drugs that **inhibit drug-metabolizing enzymes**.
- Such inhibitors of drug-metabolizing enzymes include
  - **Ketoconazole**
  - **Cimetidine**
  - **Disulfiram**
  - **Erythromycin**
  - **furanocoumarins** (in grapefruit juice)
  - **Quinidine**
  - **Ritonavir**
  - **Sulfonamides**
  - Many others.



- **The CYP3A4 isozyme of cytochrome P450, the dominant form in the human liver, is particularly sensitive to such inhibitory actions.**

Interactions Based on Metabolic Clearance

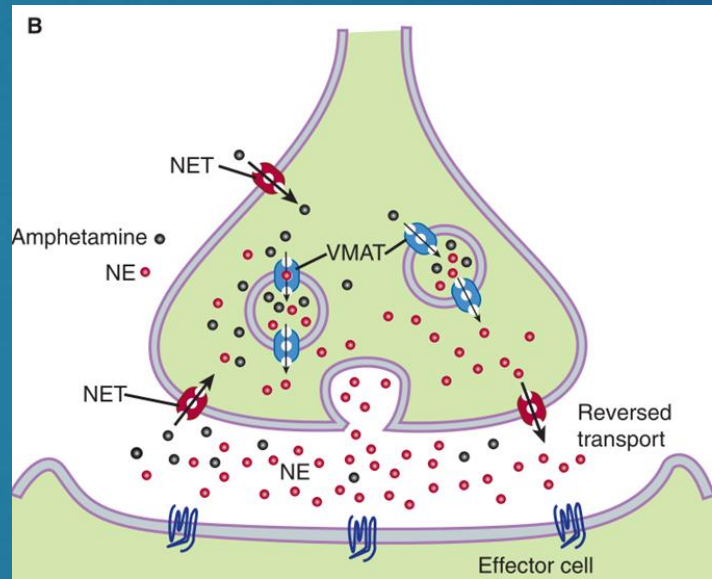
- Drugs that **reduce hepatic blood flow** (e.g., **propranolol**) may **reduce** the **clearance of other drugs metabolized in the liver**, especially those subject to flow-limited hepatic clearance such as **morphine** and **verapamil**.



Interactions Based on Metabolic Clearance

- A modified form of an interaction based on metabolic clearance results from the **ability of some drugs to increase the stores of endogenous substances by blocking their metabolism**.

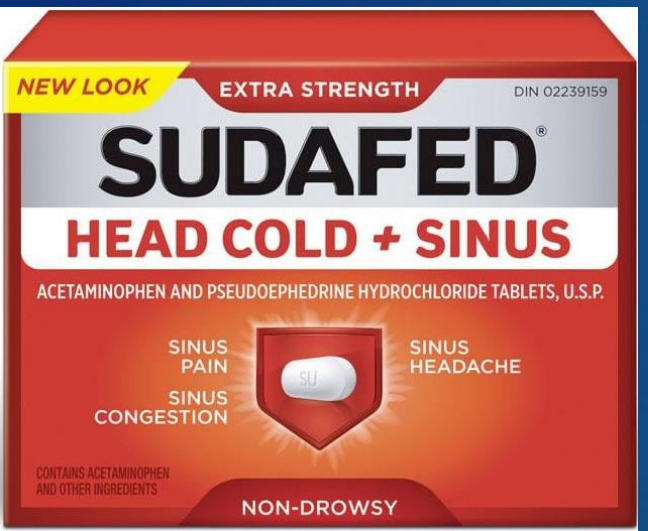
- **These endogenous compounds may subsequently be released by other exogenous drugs, resulting in an unexpected action.**

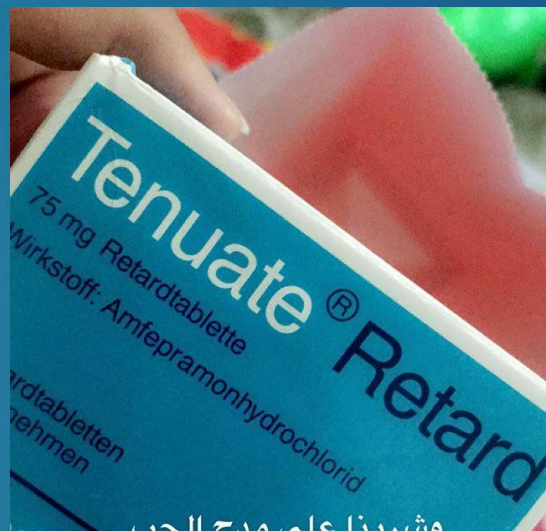


Interactions Based on Metabolic Clearance

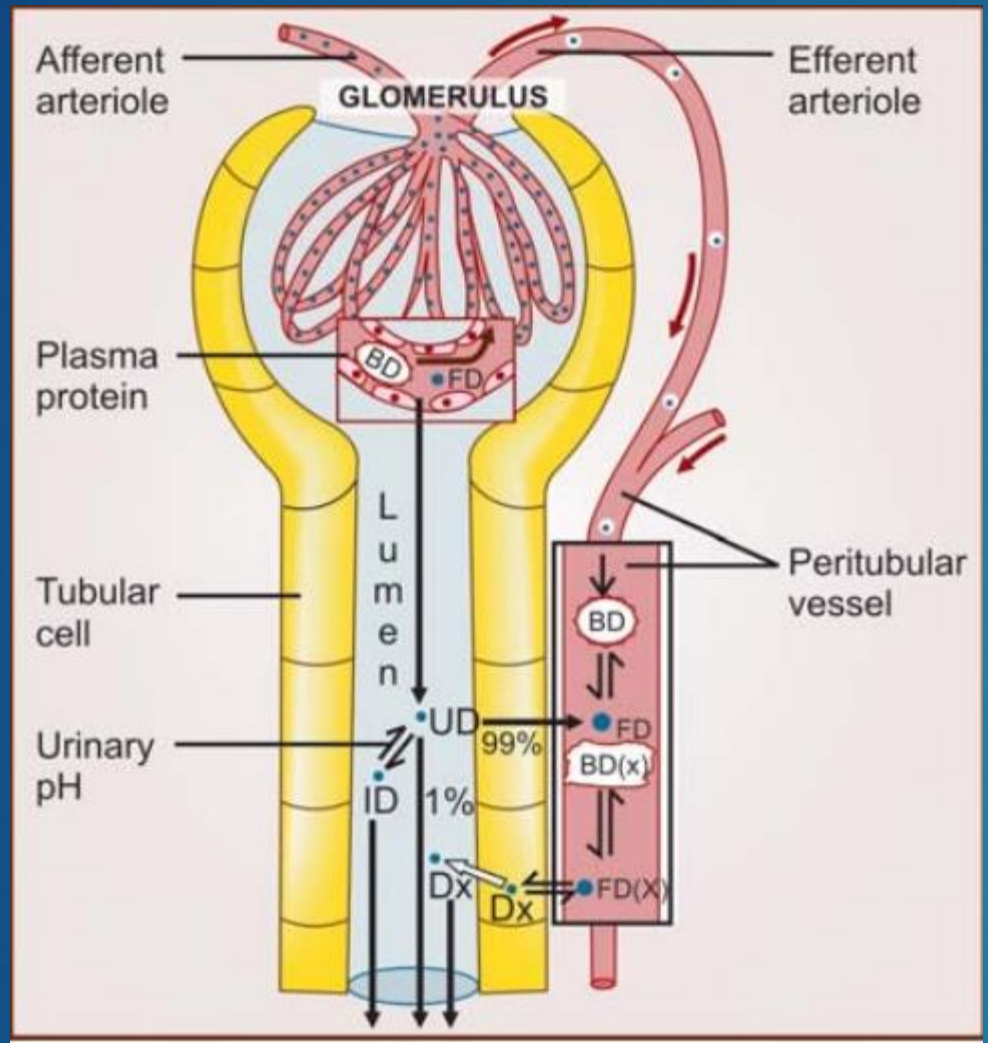
- The best-documented reaction of this type is the sensitization of patients taking **MAO inhibitors** to indirectly acting sympathomimetics (e.g., amphetamine, phenylpropanolamine).

- Such patients may suffer a **severe hypertensive** reaction in response to ordinary doses of cold remedies, decongestants, and appetite suppressants.





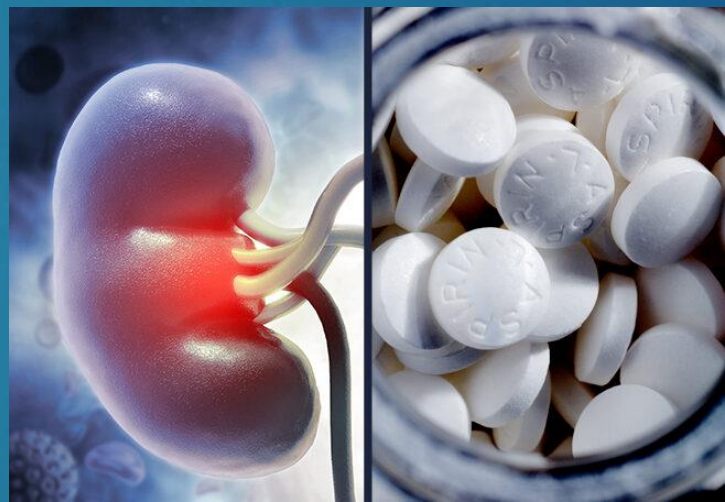
Interactions Based on Renal Function



Interactions Based on Renal Function

- Excretion of drugs by the kidney can be changed by
  - Drugs that **reduce** renal blood flow (e.g., **β blockers**)
  - **Inhibit specific renal transport mechanisms** (e.g., the action of **aspirin** on uric acid secretion in the proximal tubule)

- Drugs that **alter urinary pH** can **alter the ionization** state of drugs that are **weak acids** or **weak bases**, leading to **changes in renal tubular reabsorption**.



PHARMACODYNAMIC INTERACTIONS

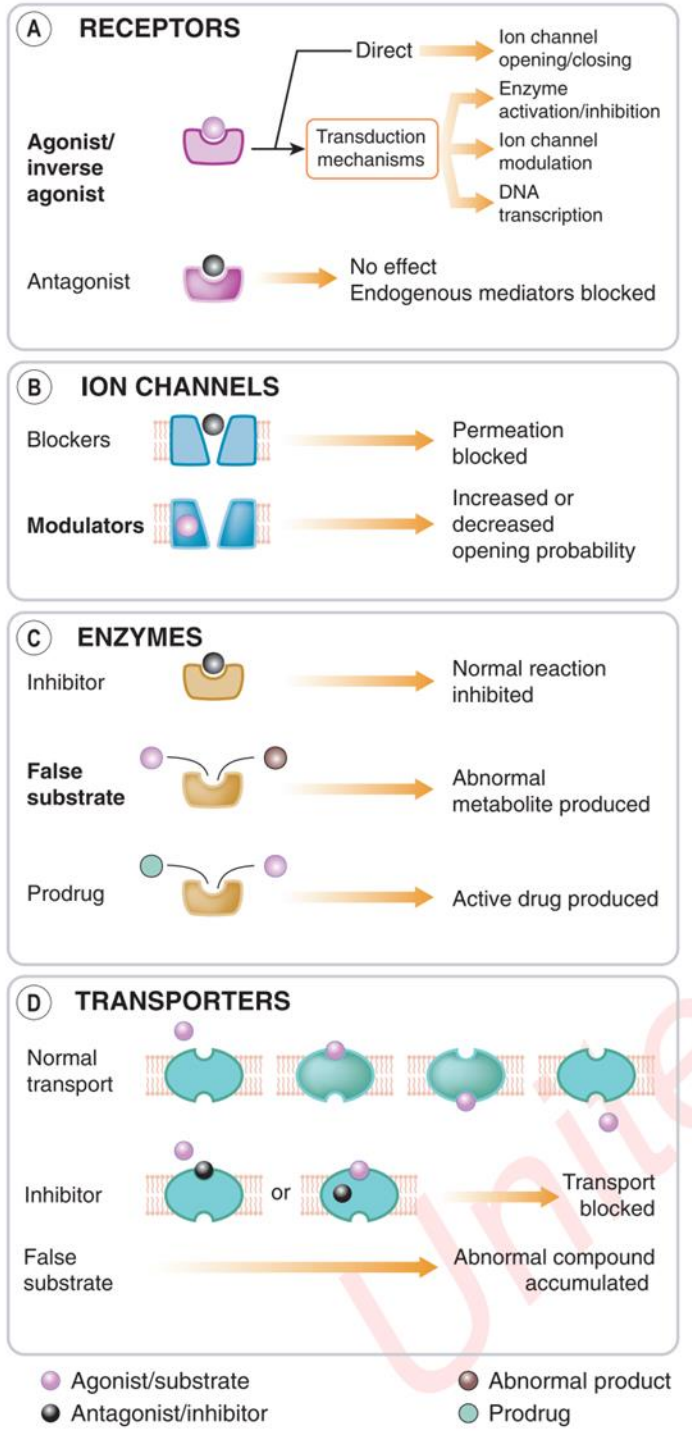
Interactions Based on Opposing Actions or Effects

Interactions Based on Opposing Actions or Effects

- **Antagonism**, the simplest type of drug interaction, is often predictable

- Antagonism of the **bronchodilating effects of β2-adrenoceptor activators** used in **asthma** is to be anticipated if a **β blocker** is given for another condition.

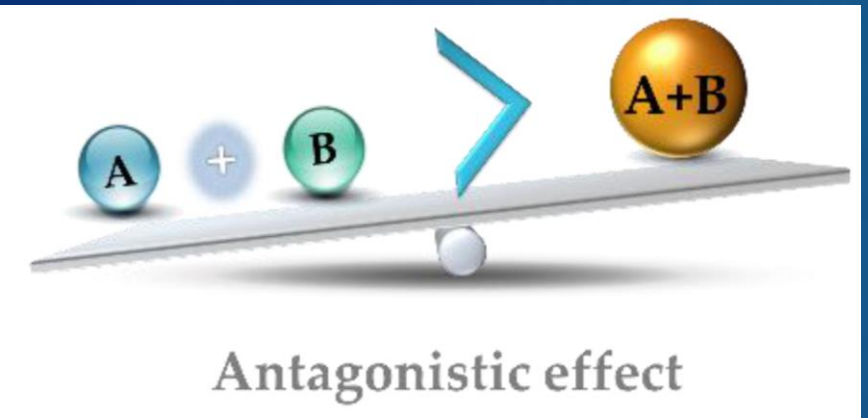
- The action of a **catecholamine on heart rate (via β-adrenoceptor activation)** is **antagonized** by an **inhibitor of acetylcholinesterase that acts through acetylcholine (via muscarinic receptors)**



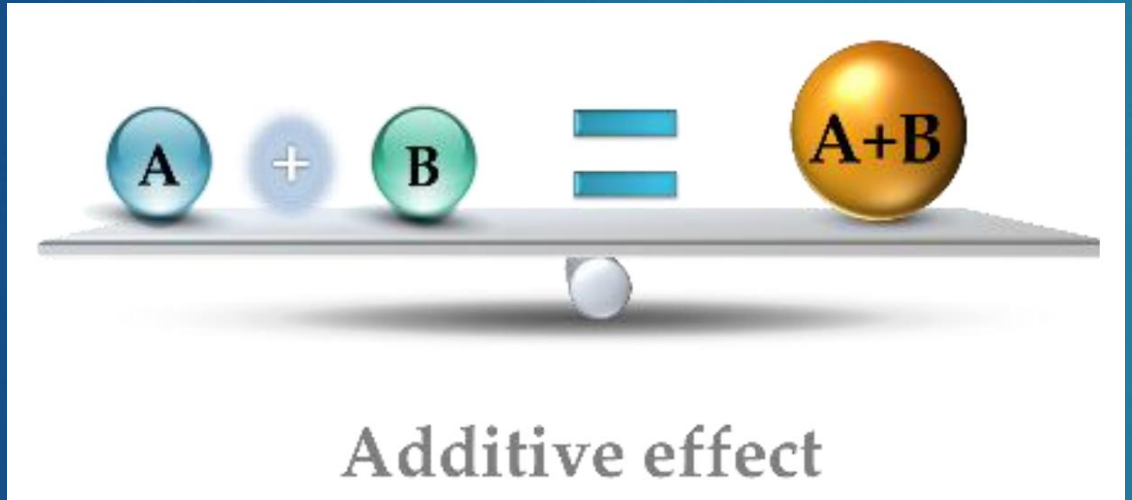
Interactions Based on Opposing Actions or Effects

- Antagonism by **mixed agonist-antagonist drugs (eg, pentazocine)** or by **partial agonists (eg, pindolol)** is **not as easily predicted** but should be expected when such drugs are used with **pure agonists**.

- Some drug antagonisms do **not** appear to be based on **receptor** interactions.
  - For example, nonsteroidal anti-inflammatory drugs (**NSAIDs**) may **decrease the antihypertensive action** of angiotensin-converting enzyme (ACE) inhibitors by **reducing renal elimination of sodium**.



Interactions Based on Additive Effects



Interactions Based on Additive Effects

- **Additive** interaction describes the **algebraic summing** of the effects of 2 drugs
- The 2 drugs **may or may not** act on the **same receptor** to produce such effects
- The combination of **tricyclic antidepressants with diphenhydramine or promethazine** predictably causes **excessive atropine-like effects** because all these drugs have significant muscarinic receptor-blocking actions
- Tricyclic antidepressants may increase the **pressor responses to sympathomimetics** by interference with amine transporter systems.

Interactions Based on Additive Effects

- One of the most common and important drug interactions is the **additive depression of CNS function** caused by concomitant administration of **sedatives, hypnotics, and opioids with each other or associated with the consumption of ethanol**

- Similarly, the patient with **moderate to severe hypertension** maintained on one drug is at **risk of excessive lowering of blood pressure** if another drug with a different site of action is added at high dosage

Interactions Based on Additive Effects

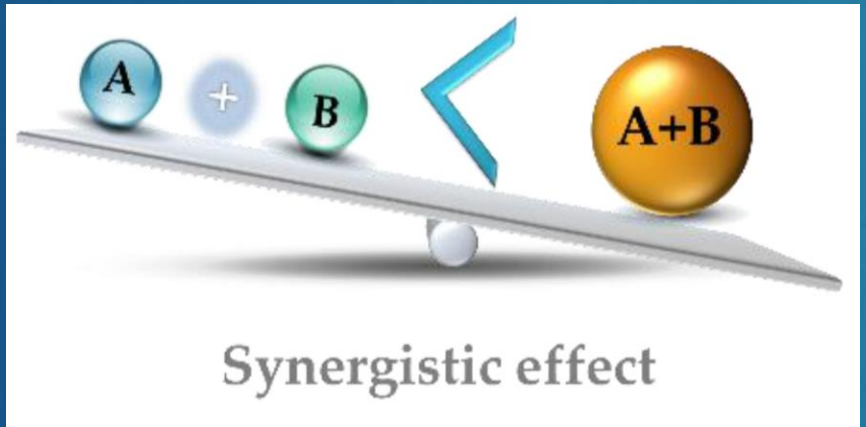
- Additive effects of **anticoagulant drugs** can lead to bleeding complications.

- **Warfarin**, the potential for such adverse effects is enhanced by
  - **Aspirin** (via an antiplatelet action)
  - **Thrombolytics** (via plasminogen activation)
  - **Thyroid hormones** (via enhanced clotting factor catabolism)

Interactions Based on Synergistic Effects

- **Supra-additive interactions and potentiation** appear to be much **less** common than antagonism and the simple additive interactions described previously

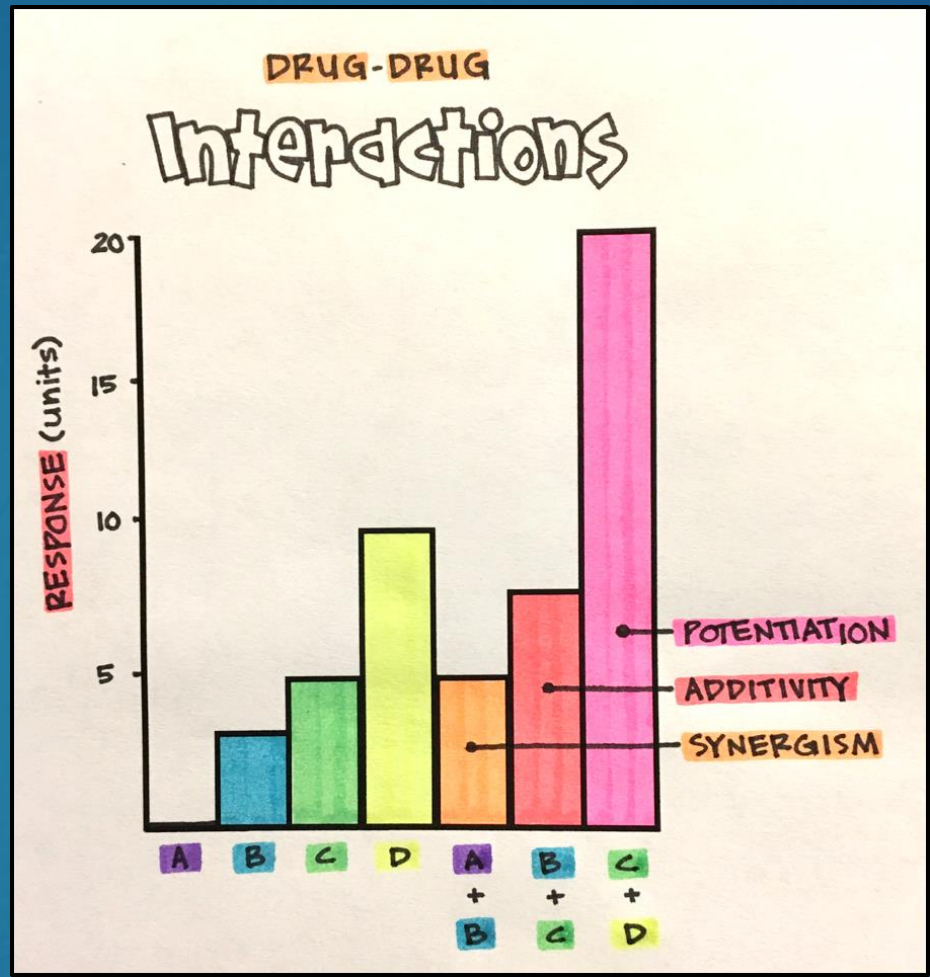
- Supra-additive (**synergistic**) interaction is said to occur when the **result of interaction** is **greater than the sum of the drugs used alone**;
  - **Certain antibiotic combinations** such as sulfonamides and dihydrofolic acid reductase inhibitors such as trimethoprim



Interactions Based on Synergistic Effects

- **Potentiation** is said to occur when **a drug's effect is increased by another agent that has no such effect**.

- Therapeutic interaction of **β-lactamase inhibitors such as clavulanic acid with β-lactamase susceptible penicillins.**



Some important drug interactions

Interaction	Potential effect	Time to effect	Recommendations and comments
Warfarin plus ciprofloxacin , clarithromycin, erythromycin, metronidazole or trimethoprim-sulfamethoxazole	Increased effect of warfarin	Generally within 1 week	Select alternative antibiotic.
Warfarin plus acetaminophen	Increased bleeding, increased INR	Any time	Use lowest possible acetaminophen dosage and monitor INR.
Warfarin plus acetylsalicylic acid	Increased bleeding, increased INR	Any time	Limit aspirin dosage to 100 mg per day and monitor INR.
Warfarin plus NSAID	Increased bleeding, increased INR	Any time	Avoid concomitant use if possible; if coadministration is necessary, use a cyclooxygenase-2 inhibitor and monitor INR.
Fluoroquinolone plus divalent/trivalent cations or sucralfate	Decreased absorption of fluoroquinolone	Any time	Space administration by 2 to 4 hours.
Carbamazepine plus cimetidine, erythromycin, clarithromycin or fluconazole	Increased carbamazepine levels	Generally within 1 week	Monitor carbamazepine levels.
Phenytoin plus cimetidine, erythromycin, clarithromycin or fluconazole	Increased phenytoin levels	Generally within 1 week	Monitor phenytoin levels.
Phenobarbital plus cimetidine, erythromycin, clarithromycin or fluconazole	Increased phenobarbital levels	Generally within 1 week	Clinical significance has not been established. Monitor phenobarbital levels.

Some important drug interactions

Interaction	Potential effect	Time to effect	Recommendations and comments
Phenytoin plus rifampin	Decreased phenytoin levels	Generally within 1 week	Clinical significance has not been established. Monitor phenytoin levels.
Phenobarbital plus rifampin	Decreased phenobarbital levels	Generally within 1 week	Monitor phenobarbital levels.
Carbamazepine plus rifampin	Decreased carbamazepine levels	Generally within 1 week	Clinical significance has not been established. Monitor carbamazepine levels.
Lithium plus NSAID or diuretic	Increased lithium levels	Any time	Decrease lithium dosage by 50% and monitor lithium levels.
Oral contraceptive pills plus rifampin	Decreased effectiveness of oral contraception	Any time	Avoid if possible. If combination therapy is necessary, have the patient take an oral contraceptive pill with a higher estrogen content (>35 μg of ethinyl estradiol) or recommend alternative method of contraception.
Oral contraceptive pills plus antibiotics	Decreased effectiveness of oral contraception	Any time	Avoid if possible. If combination therapy is necessary, recommend use of alternative contraceptive method during cycle.
Oral contraceptive pills plus troglitazone	Decreased effectiveness of oral contraception	Any time	Have the patient take an oral contraceptive pill with a higher estrogen content or recommend alternative method of contraception.
Cisapride plus erythromycin, clarithromycin, fluconazole, itraconazole, ketoconazole, nefazodone, indinavir or ritonavir	Prolongation of QT interval along with arrhythmias secondary to inhibited cisapride metabolism	Generally within 1 week	Avoid. Consider whether metoclopromide therapy is appropriate for the patient.
Cisapride plus class IA or class III antiarrhythmic agents, tricyclic antidepressants or phenothiazine	Prolongation of QT interval along with arrhythmias	Any time	Avoid. Consider whether metoclopromide therapy is appropriate for the patient.

Some important drug interactions

Interaction	Potential effect	Time to effect	Recommendations and comments
Sildenafil plus nitrates	Dramatic hypotension	Soon after taking sildenafil	Absolute contraindication.
Sildenafil plus cimetidine, erythromycin, itraconazole or ketoconazole	Increased sildenafil levels	Any time	Initiate sildenafil at a 25-mg dose.
HMG-CoA reductase inhibitor plus niacin, gemfibrozil (Lopid), erythromycin or itraconazole	Possible rhabdomyolysis	Any time	Avoid if possible. If combination therapy is necessary, monitor the patient for toxicity.
Lovastatin (Mevacor) plus warfarin	Increased effect of warfarin	Any time	Monitor INR.
SSRI plus tricyclic antidepressant	Increased tricyclic antidepressant level	Any time	Monitor for anticholinergic excess and consider lower dosage of tricyclic antidepressant.
SSRI plus selegiline or nonselective monoamine oxidase inhibitor	Hypertensive crisis	Soon after initiation	Avoid
SSRI plus tramadol	Increased potential for seizures; serotonin syndrome	Any time	Monitor the patient for signs and symptoms of serotonin syndrome.
SSRI plus St. John's wort	Serotonin syndrome	Any time	Avoid
SSRI plus naratriptan , rizatriptan, sumatriptan or zolmitriptan	Serotonin syndrome	Possibly after initial dose	Avoid if possible. If combination therapy is necessary, monitor the patient for signs and symptoms of serotonin syndrome.

INTERACTIONS OF HERBAL MEDICATIONS WITH OTHER DRUGS

INTERACTIONS OF HERBAL MEDICATIONS WITH OTHER DRUGS

- Because of the marked increase in use of herbal medications, more interactions of these agents with purified drugs are being reported.

- Several herbals are known to **enhance the actions of anticoagulants.**

- Many other herbs, or edible plants, also contain compounds with **anticoagulant** or **antiplatelet** potential, including
  - Anise
  - Arnica
  - Capsicum
  - Celery
  - Chamomile
  - Clove
  - Feverfew
  - Garlic
  - Ginger
  - Horseradish
  - Turmeric
  - wild lettuce












Selected interactions of herbals with other drugs

Herbal Medication	Other Drugs	Interaction
Garlic, ginkgo	Anticoagulants, antiplatelet agents	Increased risk of bleeding
Ginseng	Antidepressants	Increased antidepressant effect, mania
Liquorice root	Aldosterone, antihypertensive drugs	Liquorice root extract (not candy) increases salt retention; hypertension
Ma huang, other ephedra preparations	Sympathomimetics	Ephedrine in ma huang is additive with other sympathomimetics; hypertension, stroke
St. John's wort	Oral contraceptives, cyclosporine, digoxin, HIV protease inhibitors, phenytoin, oral anticoagulants: (warfarin, apixaban, dabigatran, rivaroxaban)	Increased metabolism of drug, decreased efficacy
	Antidepressants	Increased antidepressant effect; serotonin syndrome with selective serotonin reuptake inhibitors (SSRIs and SNRIs)

How to interpret drug interactions

Onset

- **Rapid – within 24 hours**
- **Delayed – days to weeks**

- **Severity**
  - **Major – life-threatening or permanent damage**
  - **Moderate – deterioration of patient's status**
  - **Minor – bothersome or little effect**

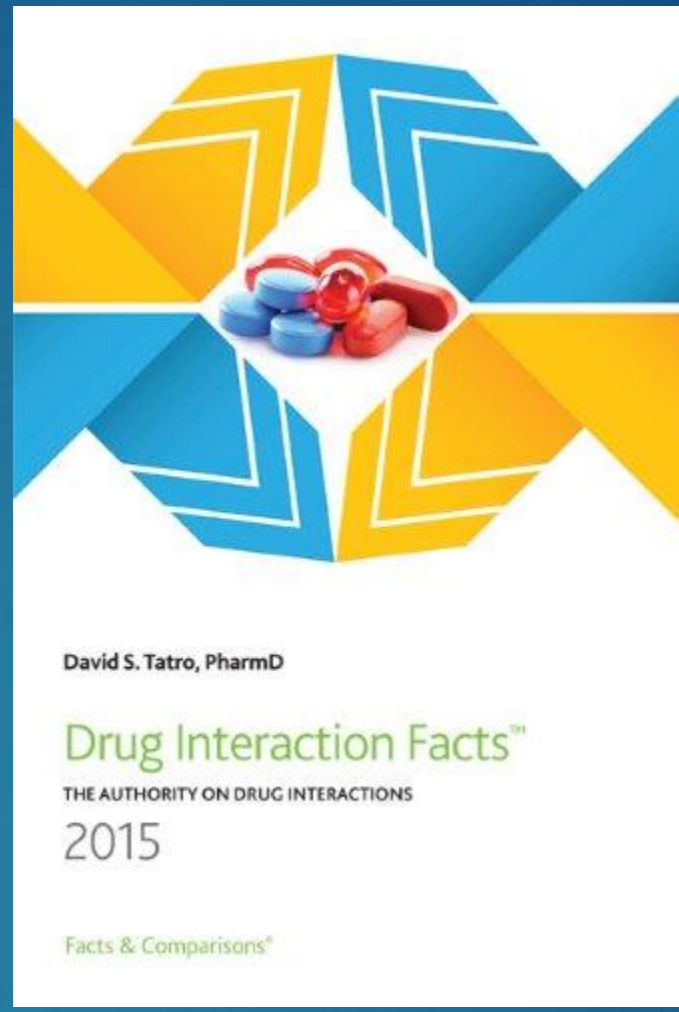
- **Documentation**
- **The confidence that an interaction can occur. This evaluation is based on supporting biomedical literature. The Discussion in each monograph provides specific comments on the data reviewed.**
  - **Established – proven to occur in well-controlled studies**
  - **Probable – very likely, but not proven clinically**
  - **Suspected – may occur; some good data, but needs more study**
  - **Possible – could occur, but data are very limited**
  - **Unlikely – doubtful; no good evidence of a clinical effect**

How to interpret drug interactions

1 is a severe and well-documented interaction.

5 is an interaction of no more than unlikely or possible documentation.

Significance Rating	Severity	Documentation
1	Major	Suspected or >
2	Moderate	Suspected or >
3	Minor	Suspected or >
4	Major/Moderate	Possible
5	Minor	Possible
	Any	Unlikely



How to interpret drug interactions

X	Avoid combination	C	Monitor therapy	A	No known interaction
D	Consider therapy modification	B	No action needed	*More about Risk Ratings*	▼

X Sildenafil (Phosphodiesterase 5 Inhibitors) Vasodilators (Organic Nitrates)

Risk Rating X: Avoid combination

Summary Phosphodiesterase 5 Inhibitors may enhance the vasodilatory effect of Vasodilators (Organic Nitrates). **Severity** Major **Reliability Rating** Excellent

Patient Management Concurrent use of phosphodiesterase 5 (PDE5) inhibitors with an organic nitrate is contraindicated; this includes both regular and intermittent nitrate use. Nitrate treatment should be delayed if a patient who has taken a PDE5 inhibitor develops chest pain. The delay should be at least 12 hours if the patient has taken avanafil and at least 48 hours if they have taken tadalafil. A sufficient time between administration of other PDE5 inhibitors and nitrates has not been determined, although a consensus statement suggests the delay should be at least 24 hours for sildenafil. Longer delays may be required for patients taking CYP3A4 inhibitors as the clearance and elimination of the PDE5 inhibitor would be delayed.

Phosphodiesterase 5 Inhibitors Interacting Members Avanafil*, Mirodenafil, Sildenafil*, Tadalafil*, Udenafil, Vardenafil*

Vasodilators (Organic Nitrates) Interacting Members Isosorbide Dinitrate, Isosorbide Mononitrate, Nicorandil, Nitroglycerin*

X FLUoxetine (Selective Serotonin Reuptake Inhibitors) Selegiline

Risk Rating X: Avoid combination

Summary Selective Serotonin Reuptake Inhibitors may enhance the serotonergic effect of Selegiline. This could result in serotonin syndrome. **Severity** Major **Reliability Rating** Fair

Patient Management Avoid concomitant use of selegiline and SSRIs. At least 14 days should elapse between discontinuation of selegiline and initiation of treatment with an SSRI. In patients taking SSRIs with a long half-life (eg, fluoxetine and its active metabolite), allow at least five weeks (perhaps longer, especially if fluoxetine has been prescribed chronically and/or at higher doses) to elapse between discontinuation of the SSRI and initiation of selegiline. This combination is specifically contraindicated in the transdermal selegiline prescribing information.

Selective Serotonin Reuptake Inhibitors Interacting Members Citalopram, Dapoxetine, Escitalopram, FLUoxetine, FluvoxaMINE, PARoxetine, Sertraline, Vilazodone, Vortioxetine

How to interpret drug interactions

X	Avoid combination	C	Monitor therapy	A	No known interaction
D	Consider therapy modification	B	No action needed	*More about Risk Ratings*	▼

C Warfarin (Vitamin K Antagonists)
Acetaminophen

Risk Rating C: Monitor therapy

Summary Acetaminophen may enhance the anticoagulant effect of Vitamin K Antagonists. This appears most likely with daily acetaminophen doses exceeding 1.3 or 2 g/day for multiple consecutive days. **Severity** Moderate **Onset** Delayed (Sequence Important) **Reliability Rating** Good

Patient Management Monitor for increased therapeutic effects of anticoagulants if acetaminophen is initiated/dose increased, or decreased effects if acetaminophen is discontinued/dose decreased. This may be of particular concern in patients expected to take, or who have been taking, more than 1.3 to 2 g/day of acetaminophen for for several consecutive days. Advise patients to limit acetaminophen intake to short-term treatment of acute illnesses when possible and to report any regular use to the clinician who is monitoring their anticoagulant therapy. Use for more than 3 consecutive days may warrant additional INR testing.

D Warfarin (Vitamin K Antagonists)
Ibuprofen (Nonsteroidal Anti-Inflammatory Agents (Nonselective))

Risk Rating D: Consider therapy modification

Summary Nonsteroidal Anti-Inflammatory Agents (Nonselective) may enhance the anticoagulant effect of Vitamin K Antagonists. **Severity** Moderate **Onset** Delayed **Reliability Rating** Fair

Patient Management Patients receiving vitamin K antagonist anticoagulants should be instructed to not initiate nonsteroidal anti-inflammatory agent (NSAID)-containing medicines without consulting their healthcare professional. Acetaminophen is usually a good antipyretic and analgesic choice for patients taking oral anticoagulants, though some reports do describe changes in INR with acetaminophen. Monitor for increased signs and symptoms of bleeding if a vitamin K antagonist and an NSAID are used concomitantly.

Nonsteroidal Anti-Inflammatory Agents (Nonselective) Interacting Members Aceclofenac, Acemetacin, Clonixin, Dexibuprofen, Dexketoprofen, Diclofenac (Systemic), Diflunisal*, Dipyrone, Etodolac, Fenbufen, Fenoprofen, Flurbiprofen (Systemic), Ibuprofen*, Indomethacin, Ketoprofen*, Ketorolac (Nasal), Ketorolac (Systemic), Lornoxicam, Loxoprofen, Meclofenamate, Mefenamic Acid*, Meloxicam, Nabumetone, Naproxen, Oxaprozin, Pelubiprofen, Phenylbutazone, Piroxicam (Systemic)*, Propyphenazone, Sulindac*, Tenoxicam, Tiaprofenic Acid, Tolfenamic Acid, Tolmetin*, Zaltoprofen

Vitamin K Antagonists Interacting Members Acenocoumarol, Phenindione, Phenprocoumon [INT], Warfarin*

How to interpret drug interactions

X	Avoid combination	C	Monitor therapy	A	No known interaction
D	Consider therapy modification	B	No action needed	*More about Risk Ratings*	▼

D Ciprofloxacin (Systemic) (Quinolones)
Calcium Carbonate (Calcium Salts)

Dependencies

- **Route** (oral): Only oral preparations of quinolone antibiotics and calcium salts are expected to participate in this interaction.

Risk Rating D: Consider therapy modification

Summary Calcium Salts may decrease the absorption of Quinolones. Of concern only with oral administration of both agents. **Severity** Moderate **Reliability Rating** Excellent

Patient Management Consider administering an oral quinolone at least 2 hours before, or 6 hours after, the dose of an oral calcium supplement to minimize this interaction and the risk of reduced absorption. Monitor for decreased therapeutic effects of oral quinolones if administered with oral calcium supplements.

C Warfarin (Vitamin K Antagonists)
Ciprofloxacin (Systemic) (Quinolones)

Risk Rating C: Monitor therapy

Summary Quinolones may enhance the anticoagulant effect of Vitamin K Antagonists. **Severity** Moderate **Reliability Rating** Good

Patient Management Monitor for increased INR/prothrombin time (PT) and/or toxic effects of warfarin or acenocoumarol if a quinolone antibiotic is initiated (especially during the first few days of concomitant therapy) or the dose is increased, or for decreased effects if a quinolone antibiotic is discontinued or its dose is decreased.

Quinolones Interacting Members Ciprofloxacin (Systemic), Delafloxacin, Enoxacin, Gemifloxacin, LevoFLOXacin (Oral Inhalation), LevoFLOXacin (Systemic), Levonadifloxacin, Lomefloxacin, Moxifloxacin (Systemic), Nalidixic Acid*, Norfloxacin*, Ofloxacin (Systemic), Pefloxacin, Pipemidic Acid, Prulifloxacin, Sparfloxacin, Zabofloxacin

Vitamin K Antagonists Interacting Members Acenocoumarol, Phenindione, Phenprocoumon [INT], Warfarin*

How to interpret drug interactions

X Warfarin (Vitamin K Antagonists)
Tamoxifen

Risk Rating X: Avoid combination

Summary Tamoxifen may increase the serum concentration of Vitamin K Antagonists. **Severity** Major **Reliability Rating** Fair

Patient Management Combined use of tamoxifen with warfarin is contraindicated in U.S. labeling due to risk of excessive anticoagulant response and resultant increased risk of bleeding. It is expected that tamoxifen would interact with other coumarin derivatives in a similar manner. Of note, this combination is not specifically contraindicated in some non-U.S. labeling.

Vitamin K Antagonists Interacting Members Acenocoumarol, Phenindione, Phenprocoumon [INT], Warfarin

Discussion Increased anticoagulant response to warfarin and/or clinically significant bleeding episodes with the combination of tamoxifen and warfarin have been described in various case reports and case series.[1,2,3,4] While warfarin was discontinued in some cases, in those in which the combination was continued, significant reductions in warfarin dose requirements (of approximately 35-60%) were noted. In a review of 31 patients receiving this combination, 8 patients experienced documented bleeding complications.[5]

X Lithium (Serotonergic Agents (High Risk, Miscellaneous))
Monoamine Oxidase Inhibitors (Type B)

Risk Rating X: Avoid combination

Summary Monoamine Oxidase Inhibitors (Type B) may enhance the serotonergic effect of Serotonergic Agents (High Risk, Miscellaneous). This could result in serotonin syndrome. **Severity** Major **Reliability Rating** Fair

Patient Management Avoid concomitant use of type B monoamine oxidase inhibitors with lithium or tryptophan. At least 14 days should elapse between discontinuation of type B MAOIs and initiation of lithium or tryptophan.

Monoamine Oxidase Inhibitors (Type B) Interacting Members Rasagiline, Safinamide, Selegiline

Serotonergic Agents (High Risk, Miscellaneous) Interacting Members Lithium, Tryptophan

Discussion Data characterizing serotonergic risks of combining type B monoamine oxidase inhibitors (MAOIs) with lithium or tryptophan are not available. However, there is evidence that the individual drugs can contribute to the development of serotonin syndrome/serotonin toxicity (SS/ST), and a representative selection of that evidence is described here. Numerous case reports describe patients who experienced SS/ST with the combination of a single serotonergic agent (eg, SSRI, SNRI, TCA) and selegiline,[1,2,3] rasagiline,[4,5,6] safinamide,[7] lithium,[8,9,10,11] or tryptophan.[12,13,14]

Prescribing information for type B MAOIs do not specifically address use with lithium or tryptophan, but all state that concomitant use with other serotonergic agents is either not recommended or contraindicated.[7,15,16] At least 14 days should elapse between discontinuation of type B MAOIs and initiation of serotonergic agents such as lithium or tryptophan.[7,15,16]

Many drugs possess an ability to enhance central serotonergic activity (eg, inhibition of serotonin reuptake, decreased serotonin metabolism, direct serotonin receptor stimulation) either as an intended mechanism of action or as an additional effect. The concomitant use of 2 or more of these agents may increase the risk for serotonin toxicity (also called serotonin syndrome), a condition of serotonergic overstimulation characterized by autonomic, neuromuscular, and neurologic effects.[17,18,19]

C

FLUoxetine (Serotonergic Agents (High Risk)) St John's Wort

Risk Rating C: Monitor therapy

Summary St John's Wort may enhance the serotonergic effect of Serotonergic Agents (High Risk). This could result in serotonin syndrome. St John's Wort may decrease the serum concentration of Serotonergic Agents (High Risk). **Severity** Major **Reliability Rating** Fair

Patient Management Monitor for signs and symptoms of serotonin syndrome/serotonin toxicity (eg, hyperreflexia, clonus, hyperthermia, diaphoresis, tremor, autonomic instability, mental status changes) when St. John's wort is combined with high risk serotonergic agents. Patients with other risk factors (eg, higher drug concentrations/doses, greater numbers of serotonergic agents) are likely at greater risk for these potentially life-threatening toxicities. Additionally, monitor for decreased concentrations of serotonergic agents that are substrates of CYP3A4 (eg, citalopram, mirtazapine, vilazodone, vortioxetine).

B

Ethinyl Estradiol and Levonorgestrel (Estrogen Derivatives (Contraceptive)) Antibiotics

Risk Rating B: No action needed

Summary Antibiotics may diminish the therapeutic effect of Estrogen Derivatives (Contraceptive). **Severity** Minor **Reliability Rating** Poor

Patient Management No action required beyond standard clinical care measures.

Antibiotics Interacting Members Amikacin (Systemic), Arbekacin, Azithromycin (Systemic), Aztreonam (Systemic), Bacitracin (Systemic), Bedaquiline, Capreomycin, Cefaclor, Cefadroxil, Cefamandole, Cefatrizine, Cefazedone, CeFAZolin, Cefbuperazone, Cefcapene, Cefdinir, Cefditoren, Cefepime, Cefetamet Pivoxil, Cefiderocol, Cefixime, Cefmetazole, Cefminox, Cefodizime, Cefoperazone, Cefotaxime, CefoTEtan, Cefotiam, CefOXitin, Cefpiramide, Cefpirome, Cefpodoxime, Cefprozil, Cefroxadine, Ceftaroline Fosamil, CefTAZidime, Ceftezole, Ceftibuten, Ceftizoxime, Ceftobiprole, Ceftolozane, CefTRIAXone, Cefuroxime, Cephalexin, Cephaloridine, Cephalothin, Cephradine, Chloramphenicol (Systemic), Ciprofloxacin (Systemic), Clarithromycin, Clindamycin (Systemic), Clofazimine, Colistimethate, CycloSERINE, Dalbavancin, Dapsone (Systemic), DAPTOmycin, Delafloxacin, Delamanid, Doripenem, Enoxacin, Ertapenem, Erythromycin (Systemic), Ethambutol, Ethionamide, Fidaxomicin, Flomoxef, Fosfomycin, Fusidic Acid (Systemic), Gemifloxacin, Gentamicin (Systemic), Imipenem, Isepamicin, Isoniazid, Ivermectin (Systemic), Kanamycin, Lefamulin, Lefamulin (Intravenous), LevoFLOXacin (Oral Inhalation), LevoFLOXacin (Systemic), Levonadifloxacin, Lincomycin, Linezolid, Lomefloxacin, Mafenide, Meropenem, Methenamine, Methylol Cephalexin, MetroNIDAZOLE (Systemic), Moxifloxacin (Systemic), Nalidixic Acid, Neomycin (Systemic), Netilmicin (Systemic), Nifuroxazide, Nitrofurantoin, Nitroxoline [INT], Norfloxacin, Ofloxacin (Systemic), Oritavancin, Ornidazole, Paromomycin, Pefloxacin, Pentamidine (Systemic), Pipemidic Acid, Plazomicin, Polymyxin B, Prothionamide, Prulifloxacin, Pyrazinamide, Quinupristin and Dalfopristin, Ribostamycin, Rifamycin, RifAXIMin, Roxithromycin, Secnidazole, Sisomicin, Sparfloxacin, Spiramycin, Streptomycin, Sulbactam, SulfADIAZINE, Sulfadoxine, Sulfamethoxazole, SulfiSOXAZOLE, Taurolidine, Tedizolid, Teicoplanin, Telavancin, Telithromycin, Terizidone, Tinidazole, Tobramycin (Systemic), Trimethoprim, Vancomycin, Zabofloxacin

Exceptions (agents listed are discussed in separate interaction monograph[s] or are non-interacting) Amoxicillin, Ampicillin, Bacampicillin, Cloxacillin, Demeclocycline, Dicloxacillin, Doxycycline, Eravacycline, Flucloxacillin, Lymecycline, Minocycline (Systemic), Nafcillin, Omadacycline, Oxacillin, Oxytetracycline, Penicillin G (Parenteral/Aqueous), Penicillin G Benzathine, Penicillin G Procaine, Penicillin V Benzathine, Penicillin V Potassium, Piperacillin, Pivmecillinam, Rifabutin, RifAMPin, Rifapentine, Sarecycline, Temocillin, Tetracycline (Systemic), Tigecycline

Thanks for your attention