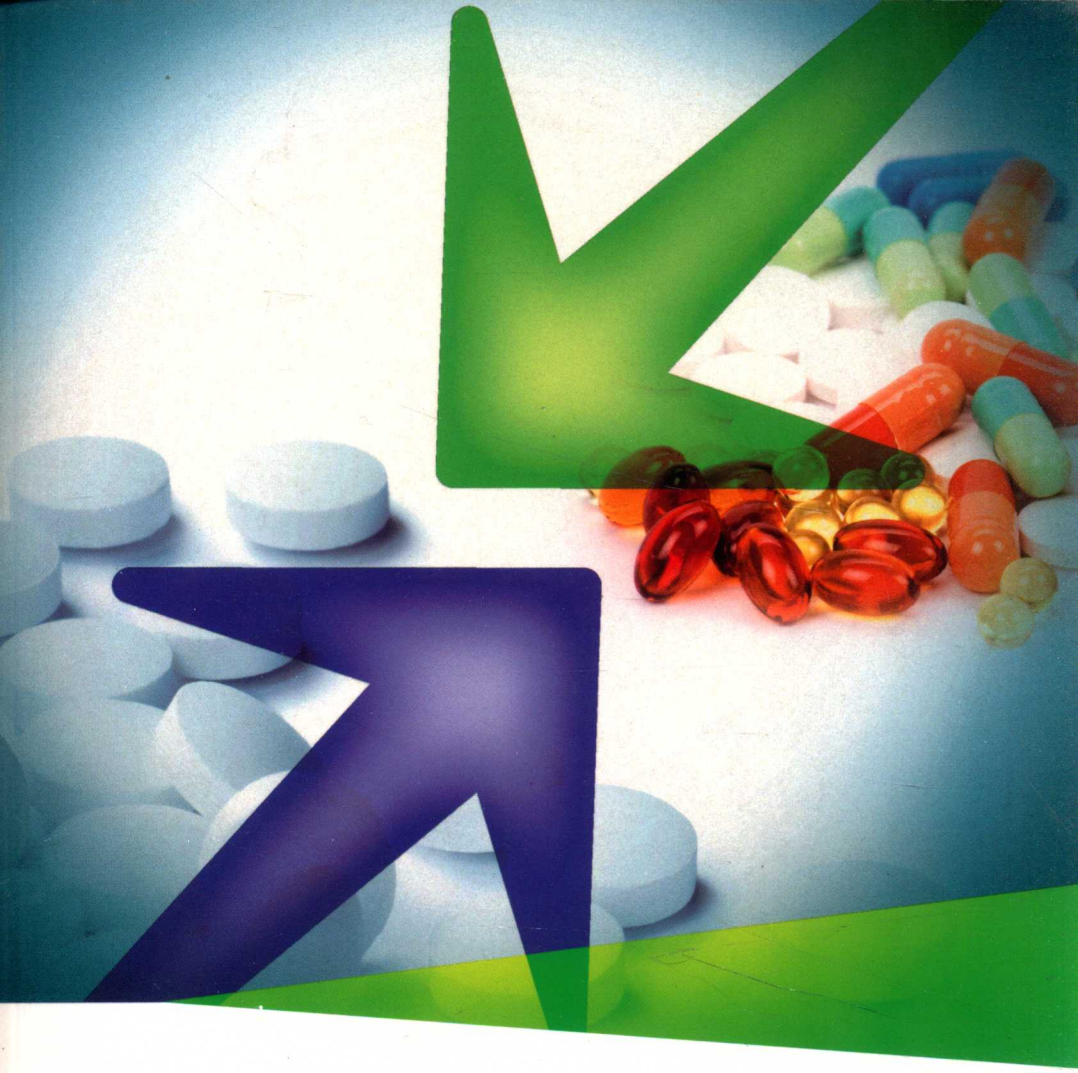


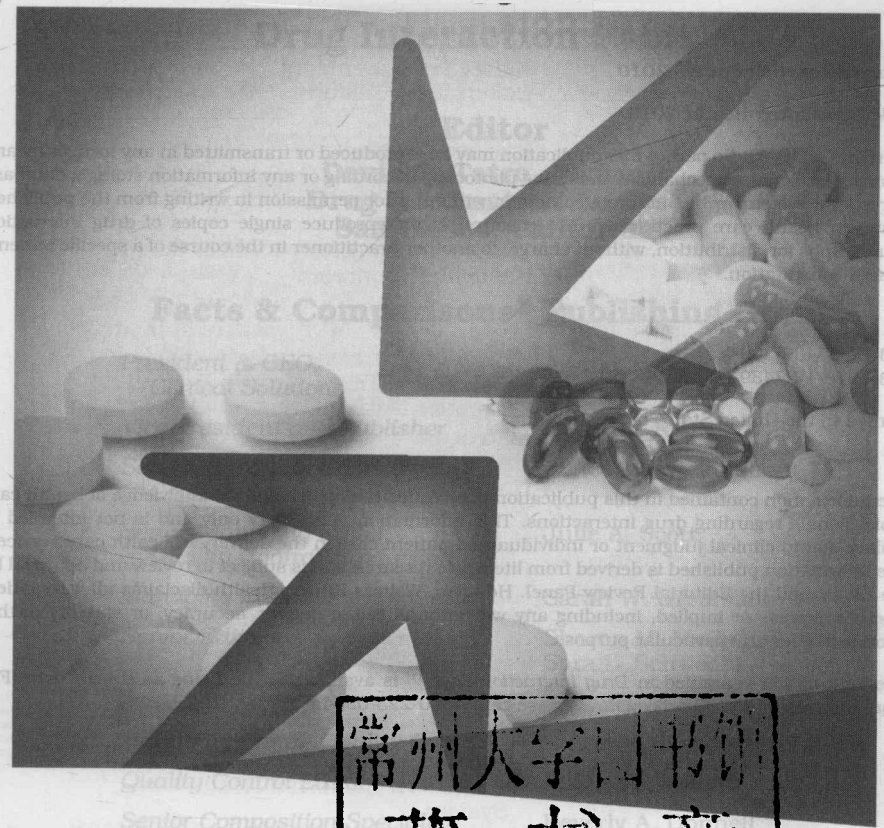
David S. Tatro, PharmD

Drug Interaction Facts™

THE AUTHORITY ON DRUG INTERACTIONS

2010

Wolters Kluwer Health | Facts & Comparisons®



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Drug Interaction Facts™

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Preface

Wolters Kluwer Health is proud to publish *Drug Interaction Facts*™ as an authoritative resource providing current drug interaction information in a concise and practical manner. This reference continues the Facts & Comparisons® line of practical, up-to-date drug information with the superb database developed by the Editor and Editorial Review Panel.

The Data: *Drug Interaction Facts*™ is based on the most current published biomedical information and has been critically evaluated to ensure the accuracy and proper interpretation of the data. The Editorial Group places a strong emphasis on establishing the clinical *relevance* of the data to make its practical utility a priority. This information is intended to supplement the knowledge of health care professionals regarding drug interactions; it is advisory only and is not intended to replace sound clinical judgment or individualized patient care.

Practical Utility: In the ongoing development of this reference, we place an emphasis on the presentation of the data to enhance therapeutic decision making. For your convenience, the index includes the significance rating for each interaction next to each entry. In addition, each individual monograph is designed to represent a logical progression of information, allowing the practitioner easy review of the desired information.

1. A significance rating provides a relative ranking of the interaction.
2. The significance of the interaction is divided into three categories:

   Onset - Severity - Documentation
3. The interaction is then summarized into its practical components:

   Effects - what will happen
   Mechanism - why it will happen
   Management - how to prevent or manage the effects of the interaction
4. Detail is provided in the Discussion concerning the available data and how assessments were made.
5. References are provided for in-depth research, if desired.

Up-to-date: The medical literature is continually monitored to identify significant new drug interaction information. The loose-leaf format of *Drug Interaction Facts*™ with quarterly supplements assures the user that the information remains up-to-date. Also available, and updated quarterly, is the *Drug Interaction Facts*™ *on Disk* program. This electronic version contains every monograph found in the book, but allows you to enter up to 20 drugs at a time to check for multiple interactions more efficiently. Finally, *Drug Interaction Facts*™ is updated monthly as part of the *Facts & Comparisons 4.0* family of on-line products.

Drug Interaction Facts™ has been designed to meet your needs. Your comments and suggestions, as always, are encouraged.

Renée Wickersham
Senior Managing Editor,
Content Development

How To Use *Drug Interaction Facts*™

Index

1. The index is the key to locating interaction monographs. Three types of entries will be found:

   Generic names – all interactions referenced (eg, Propranolol)
   Class names – all interactions referenced (eg, Beta-Adrenergic Blockers)
   Trade names – cross referenced to generic listings (eg, *Inderal*)

2. The index also identifies the significance rating of each interaction.

Features of Drug Interaction Monographs

1. **Drugs or drug classes** that may interact.

2. **Drugs** – Known and potentially interacting drugs are listed. Common trade names are given for ease of reference.

3. **Significance** –

   Significance rating – Summary of Severity and Documentation

   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

4. **Effects** – Pharmacologic effects and clinical manifestations.

5. **Mechanism** – How the interaction occurs.

6. **Management** – Recommendations for appropriate action to prevent or respond to an interaction.

7. **Discussion** – Brief review of published data and selected primary references.

Introduction

As the development of new and more potent drugs continues, determining the interactive potential of an increasingly large number of possible drug combinations becomes more complex. Pharmacists and physicians cannot be expected to know the clinical consequences of all potential drug interactions. Therefore, this reference is designed to provide comprehensive information on drug-drug and drug-food interactions in a quick reference format to enhance therapeutic decision making.

Drug Interactions

A drug-drug interaction may be defined as the pharmacologic or clinical response to the administration of a drug combination different from that anticipated from the known effects of the 2 agents when given alone. The clinical result of a drug-drug interaction may manifest as *antagonism* (ie, $1 + 1 < 2$), *synergism* (ie, $1 + 1 > 2$), or *idiosyncratic* (ie, a response unexpected from the known effects of either agent).

Drug Interaction Facts attempts to present all drug-drug and drug-food interactions that have been reasonably well documented to occur in humans. Recently, we began including significant and well-documented interactions with herbal products as well. Simple additive or antagonistic effects anticipated to occur based on known pharmacologic activity are not necessarily included. For example, the additive blood pressure lowering effects of combining two antihypertensive agents or obvious antagonistic effects of beta-blockers and isoproterenol will not be considered drug interactions.

Incidence of Drug Interactions

The clinical effects of any interaction, no matter how well documented, do not occur in every patient or at the same degree of intensity. The incidence and degree of severity of an interaction depend on both patient-related factors and information about the effects of the interaction (eg, dose-dependency, route). Patient-related factors (eg, disease process, impairment of organ function) must be individually assessed. Incidence data are included in the Discussion section of each monograph when available.

Editorial Review

Information has been compiled from primary biomedical literature. With few exceptions, only data from human subjects are considered. The Editorial Review Panel and the Editor critically evaluate all studies as to the appropriateness of the methods, procedures, and statistical analyses used. These interdisciplinary groups, comprised of physicians, pharmacologists, and clinical pharmacists, provide an authoritative consensus about the clinical relevance of the published information.

Index

A comprehensive index references all drug interaction monographs by generic drug name and by drug class name. Selected product trade names are included with cross-references to the generic listing. All interactions are indexed, with their significance rating, under both interacting drug names.

The Drug Interaction Monograph

Drug interaction monographs are arranged alphabetically according to the principal drug affected. Each drug interaction is presented in a one-page monograph, with information in a uniform format for easy reference.

Each drug interaction monograph is divided into the following sections: Interacting drugs, including generic and trade names; clinical significance (significance rating, onset, severity, and documentation); effects, mechanism, and management; and a discussion with primary references.

Interacting Drugs

Monographs are titled by generic drug names (eg, cimetidine) or as a drug class monograph (eg, protease inhibitors) when pharmacologic or pharmacokinetic similarities suggest that a group of drugs interacts in a similar manner. By grouping drugs and screening by interaction class rather than individual drugs, the number of distinct interactions is reduced to several hundred instead of several thousand.

When an interaction monograph references an interaction class (eg, protease inhibitors), a list of interacting members of the drug class appears directly below the drug class name. The list includes drugs that have been reported to interact, as well as those likely to interact, based on pharmacologic or pharmacokinetic characteristics. Known interacting drugs are designated with an asterisk (*). For example, cimetidine is known to inhibit the hepatic metabolism of diazepam, chlordiazepoxide, and their demethylated metabolites. In the *Benzodiazepines-Cimetidine* monograph, both diazepam and chlordiazepoxide are designated with an asterisk in the list of interacting drugs. Other benzodiazepines (eg, clonazepam, quazepam) that undergo dealkylation and hydroxylation via the hepatic microsomal enzyme system are expected to interact and, therefore, are listed as interacting drugs.

Conversely, oxazepam, lorazepam, and temazepam, which are benzodiazepines that are primarily metabolized by glucuronidation, do not interact with cimetidine; therefore, they are not included in the list of interacting drugs. Noninteracting members of a drug class are listed in the discussion when information indicates that a drug does not, or is not likely to, interact.

Significance

When evaluating any potential drug interaction, a primary concern is the clinical relevance or significance of the interaction. Significance relates to the type and magnitude of the effect and, subsequently, to the necessity of monitoring the patient or altering therapy to avoid potentially adverse consequences.

The primary factors that define clinical significance include: SIGNIFICANCE RATING; the time of ONSET of the effects of the interaction; the potential SEVERITY of the interaction; and the DOCUMENTATION that an interaction occurs clinically. The following discussion defines the guidelines used to designate the Onset, Severity, and Documentation levels assigned to each drug interaction.

Significance Rating 1 2 3 4 5

A number 1 through 5 will be assigned to each interaction monograph, based on the Editorial Group's assessment of the interaction's Severity and Documentation (defined below).

1 is a severe and well-documented interaction.

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

The formula for these number ratings is given in the following table:

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

Onset

How rapidly the clinical effects of an interaction can occur determines the urgency with which preventive measures should be instituted to avoid the consequences of the interaction. Two levels of onset are used:

Rapid: The effect will be evident within 24 hours of administration of the interacting drug. *Immediate action is necessary to avoid the effects of the interaction.*

Delayed: The effect will not be evident until the interacting drug is administered for a period of days or weeks. *Immediate action is not required.*

Severity

The potential severity of the interaction is particularly important in assessing the risk vs benefit of therapeutic alternatives. With appropriate dosage adjustments or modification of the administration schedule, the negative effects of most interactions can be avoided. Three degrees of severity are defined:

Major: The effects are potentially life-threatening or capable of causing permanent damage.

Moderate: The effects may cause a deterioration in a patient's clinical status. Additional treatment, hospitalization, or an extended hospital stay may be necessary.

Minor: The effects are usually mild; consequences may be bothersome or unnoticeable but should not significantly affect the therapeutic outcome. Additional treatment is usually not required.

Documentation

Documentation determines the degree of confidence that an interaction can cause an altered clinical response. This scale represents the Editorial Group's evaluation of the quality and clinical relevance of the primary literature supporting the occurrence of an interaction. However, multiple factors can influence whether

even a well-documented interaction occurs in a particular patient. The documentation does not address the incidence or frequency of the interaction; it is also independent of the potential severity of the effect of the interaction.

The following guidelines are used to establish the five Documentation levels:

Established: Proven to occur in well-controlled studies.

- An altered pharmacologic effect *has been demonstrated in well-controlled human studies* ... or ...
- A pharmacokinetic interaction *has been demonstrated in well-controlled human studies.* An altered pharmacologic response is expected based on the magnitude of the kinetic effect; clinical observations support the occurrence of the interaction.

Probable: Very likely but not proven clinically.

- A pharmacokinetic interaction has been demonstrated in well-controlled studies. Based on the magnitude of the kinetic changes and the known plasma level-response relationship of the affected drug, an altered pharmacologic response will *probably* occur ... or ...
- When controlled human experimentation is impractical, well-designed animal experiments confirm an interaction that is suggested by multiple case reports or uncontrolled studies.

Suspected: May occur; some good data; needs more study.

- A pharmacokinetic interaction has been demonstrated in well-controlled studies. Although an altered pharmacologic response *might be expected to occur* based on the magnitude of the kinetic changes, *no firm conclusion can be drawn* because a plasma level-response relationship has not been established for the affected drug ... or ...
- An altered pharmacologic response has been reported in multiple case reports or repeated uncontrolled clinical studies.

Possible: Could occur, but data are very limited.

- Although a pharmacokinetic interaction has been demonstrated, the kinetic changes are of such magnitude that it is *not possible to predict* if an altered response will occur ... or ...
- The evidence is divided as to whether an interaction exists ... or ...
- An altered pharmacologic response is suggested by limited data.

Unlikely: Doubtful; no good evidence of an altered clinical effect.

- A pharmacokinetic interaction has been demonstrated; however, based on the magnitude of kinetic change, a *pharmacologic alteration is unlikely* ... or ...
- *The bulk of documentation is of poor quality* or does not favor the existence of an interaction.
- In spite of reports of an interaction, well-controlled studies refute the existence of a clinically relevant interaction.

Drug interactions assigned Documentation levels of "Established," "Probable," or "Suspected" are considered to be reasonably well substantiated and have a significance rating of "1," "2," or "3." It is the opinion of the Editorial Group that these interactions have a reasonable probability of occurring.

Drug interactions assigned a Significance Rating of "4" or "5" have a Documentation level of "Possible" or "Unlikely" and are not substantiated. Because there is insufficient evidence supporting the existence of a clinically relevant interaction, prospective screening is probably not warranted. If an unanticipated effect occurs, the information in these monographs will be useful in reviewing what is known about these potential interactions.

Effects

Information concerning the pharmacologic effects of the interaction (eg, "the anticoagulant effects of oral anticoagulants are increased") and the clinical findings (eg, "possibly with bleeding") is included in this section. The interaction may lead to symptoms of drug toxicity or loss of therapeutic efficacy of one or both drugs. In some instances, the interacting combination will lead to effects that are unexpected based on the pharmacology of either drug.

The interactive potential of certain drug combinations may persist up to several days after one of the interacting drugs has been discontinued. Information concerning the duration of interactive potential is included in this section.

Mechanism

A brief description of the pharmacodynamic (eg, "decreased receptor sensitivity") or pharmacokinetic (eg, "decreased metabolism") mechanism by which an interacting drug affects the action of another drug is provided in this section.

Management

This section provides clinical management suggestions (eg, "may need a lower anticoagulant dose" or "give tetracycline at least 1 hour before antacids") so that the clinician can properly manage an interacting drug combination to prevent potential detrimental effects. Monitoring parameters are included when appropriate. Alternative therapy suggestions are provided when possible. Because of patient-, disease-, and drug-related variables, it is frequently impossible to provide specific management recommendations. Modification or alteration of the therapeutic regimen must be based on the practitioner's clinical assessment of each individual situation.

Discussion

A brief review and assessment of the studies used to document the interaction are provided to promote a better understanding of the incidence and magnitude of the interaction (eg, "in a controlled study of 6 patients, 5 developed severe hemorrhagic complications").

References

The principal references documenting the interaction are listed at the end of each monograph following the discussion. With few exceptions, only primary reference sources are used.

Principles of Drug Interactions

by Edward A. Hartshorn, PhD, and David S. Tatro, PharmD

A drug-drug interaction can be defined as the phenomenon that occurs when the effects or pharmacokinetics of a drug are altered by prior administration or coadministration of a second drug. The operational definition of drug interactions may also vary. Some restrict the term drug-drug interaction to adverse reactions and do not include beneficial interactions (eg, ampicillin and probenecid). Others view drug-drug interactions as only a part of the larger phenomenon of drug interactions, which includes interactions of drugs with foods (eg, fatty meals and griseofulvin), endogenous substances (eg, sulfonamides and bilirubin in neonates), herbals (eg, ginseng), environmental and industrial chemicals (eg, organophosphate insecticides and succinylcholine), and laboratory tests (eg, penicillins and *Clinitest*). *Drug Interaction Facts* is primarily comprised of adverse interactions that represent some clinical concern; it includes drug-drug interactions and drug-food interactions, while the herbal supplements and food edition includes herb-drug and food-drug interactions.

A drug interaction pair typically consists of the:

- object drug
- precipitant drug

The activity of the "object" drug is altered; the drug causing this change is the "precipitant" drug.[1] Other terms used have been "index drug" and "interacting drug," respectively.[2] *Drug Interaction Facts* is arranged alphabetically by object drug or object drug class. Occasionally, a drug may be an object drug in one interaction (eg, phenytoin-cimetidine) and a precipitant drug in another interaction (eg, doxycycline-phenytoin); rarely, both interacting drugs are affected by each other (eg, chloramphenicol-phenobarbital). With most pharmacologic interactions, there may be no object or precipitant drug, but simply a synergestic or antagonistic effect with both drugs (eg, concurrent use of several drugs with CNS depressant actions may result in excessive CNS depression).

Types of Drug Interactions

Drug interactions are frequently characterized as either pharmacokinetic or pharmacodynamic.

Pharmacokinetic

Pharmacokinetic interactions are those in which one drug alters the rate or extent of absorption, distribution, or elimination (metabolism or excretion) of another drug. This is most commonly measured by a change in one or more kinetic parameters, such as peak serum concentration, area under the concentration-time curve, half-life, total amount of drug excreted in urine, etc.

Pharmacodynamic

Pharmacodynamic interactions are those in which one drug induces a change in a patient's response to a drug without altering the object drug's pharmacokinetics. That is, one may see a change in drug action without altered plasma concentration. An example of this change is the increase in the toxicity of digoxin produced by potassium-wasting diuretics. Pharmacological interactions, that is, concurrent use of two or more drugs with similar or opposing pharmacological actions (eg, use of alcohol with an antianxiety drug and a hypnotic or antihistamine), are a

form of pharmacodynamic interactions. Some clinicians suggest that such reactions are not drug interactions and, indeed, most are not unless an adverse reaction is reported.

Mechanisms of Drug Interactions

Pharmacokinetic

Altered Absorption: Most interactions involving altered drug absorption occur in the gut. There are many mechanisms by which drugs could theoretically alter the absorption of another drug, including altered splanchnic blood flow, gut motility, gut pH, drug solubility, gut metabolism, gut flora, or gut mucosa. However, most of the clinically important interactions involve formation of a nonabsorbable complex by either chelation (eg, tetracycline or ciprofloxacin and di- or trivalent cations), adsorption (eg, lincomycin and kaolin-pectin), or ion exchange (eg, cholestyramine-warfarin). Exceptions are the increase in digoxin absorption or decreased efficacy of estrogen-containing oral contraceptives following administration of antibiotics that alter the bacterial flora of the gut. In addition, drugs may be excreted back into the GI lumen by P-glycoprotein, a product of the multidrug resistant gene that lowers intracellular drug concentrations by acting as an energy (ie, ATP)-dependent drug efflux pump.[3-5] Numerous drugs are potential substrates for the P-glycoprotein transporter (see table 1). P-glycoprotein is found in high amounts in normal tissues, including the large and small intestine, kidneys, liver (ie, biliary hepatocytes), and endothelial cells at the blood-brain barrier.[5-9] Drugs or herbal products that inhibit or induce (eg, St. John's wort and Yohimbine) P-glycoprotein (see table 2) may increase or decrease plasma concentrations of P-glycoprotein substrate. Thus, P-glycoprotein may be involved in many drug interactions occurring in the GI tract, liver, and kidney. The oral administration of a drug that is a substrate for P-glycoprotein may be secreted back into the GI lumen by P-glycoprotein.[9] Along the GI tract, P-glycoprotein concentrations are lowest in the stomach and highest in the colon.[4] If a drug is a substrate of P-glycoprotein in the GI tract, uptake from the intestine will be incomplete (ie, decreasing drug levels).[6-8] Coadministration of digoxin (eg, *Lanoxin*) and rifampin (eg, *Rifadin*) may result in a decrease in digoxin plasma concentrations. The induction of intestinal P-glycoprotein by rifampin and the subsequent secretion of digoxin back into the GI tract by P-glycoprotein has been implicated as a major mechanism of this drug interaction.[10] In eight healthy volunteers, rifampin treatment increased intestinal P-glycoprotein content 3.5-fold, which correlated with the area under the plasma concentration-time curve after oral but not IV digoxin administration.[10]

Table 1. Substrates for P-Glycoprotein [3-6,9-19]

Amiodarone (eg, *Cordarone*)	Erythromycin (eg, *Ery-Tab*)	Nifedipine (eg, *Procardia*)
Chlorpromazine (eg, *Thorazine*)	Estradiol (eg, *Estrace*)	Ondansetron (*Zofran*)
Clarithromycin (eg, *Biaxin*)	Etoposide (eg, *Vepesid*)	Paclitaxel (eg, *Taxol*)
Cyclosporine (eg, *Neoral*)	Felodipine (*Plendil*)	Progesterone (eg, *Prometrium*)
Dactinomycin (*Cosmegen*)	Fexofenadine (*Allegra*)	Promethazine (eg, *Phenergan*)
Daunorubicin (eg, *Cerubidine*)	Fluphenazine (eg, *Prolixin*)	Quinidine
Dexamethasone (eg, *Decadron*)	Hydrocortisone (eg, *Cortef*)	Reserpine
Digoxin (eg, *Lanoxin*)	Indinavir (*Crixivan*)	Ritonavir (*Norvir*)
Diltiazem (eg, *Cardizem*)	Itraconazole (eg, *Sporanox*)	Saquinavir (eg, *Fortovase*)
Doxorubicin (eg, *Adriamycin*)	Ketoconazole (eg, *Nizoral*)	Sirolimus (*Rapamune*)
	Lidocaine (eg, *Xylocaine*)	Tacrolimus (*Prograf*)
	Loperamide (eg, *Imodium*)	Tamoxifen (eg, *Nolvadex*)
	Lovastatin (eg, *Mevacor*)	Teniposide (*Vumon*)
	Mifepristone (*Mifeprex*)	Testosterone (*Delatestryl*)
	Mitoxantrone (*Novantrone*)	Trifluoperazine
	Nelfinavir (*Viracept*)	Verapamil (eg, *Calan*)
	Nicardipine (eg, *Cardene*)	Vinblastine (eg, *Velban*)
		Vincristine (eg, *Vincasar PFS*)

Table 2. Inducers and Inhibitors of P-Glycoprotein. [3-4,6-7,10,12-14,17-18]

Inducers	Inhibitors
Rifampin (eg, *Rifadin*)	Amiodarone (eg, *Cordarone*)
Ritonavir (*Norvir*)	Atorvastatin (*Lipitor*)
St. John's Wort	Chlorpromazine (eg, *Thorazine*)
Yohimbine	Clarithromycin (eg, *Biaxin*)
	Cyclosporine (eg, *Neoral*)
	Diltiazem (eg, *Cardizem*)
	Erythromycin (eg, *Ery-Tab*)
	Felodipine (*Plendil*)
	Fluphenazine (eg, *Prolixin*)
	Hydrocortisone (eg, *Cortef*)
	Indinavir (*Crixivan*)
	Itraconazole (eg, *Sporanox*)
	Ketoconazole (eg, *Nizoral*)
	Lidocaine (eg, *Xylocaine*)
	Mifepristone (*Mifeprex*)
	Nelfinavir (*Viracept*)
	Nicardipine (eg, *Cardene*)
	Nifedipine (eg, *Procardia*)
	Progesterone (eg, *Prometrium*)
	Propranolol (eg, *Inderal*)
	Quinidine
	Reserpine
	Ritonavir (*Norvir*)
	Saquinavir (eg, *Fortovase*)
	Tacrolimus (*Prograf*)
	Tamoxifen (eg, *Nolvadex*)
	Testosterone (*Delatestryl*)
	Trifluoperazine
	Verapamil (eg, *Calan*)

Altered Distribution:
Protein Binding – Once absorbed, a drug is carried via the blood to tissues and receptor sites. The amount of drug available to bind to the receptor is determined by the absorption, metabolism, excretion, and binding to inactive sites, as well as the affinity of the drug for the receptors and the drug's intrinsic activity. Of great concern are those drugs that are highly bound to plasma albumin and the potential for drug displacement from albumin binding sites upon coadministration of another highly bound drug. This is the mechanism used to explain many interactions, such as warfarin-phenylbutazone or phenytoin-valproic acid. Displacement of a drug from its inactive binding site (such as albumin) may increase the serum concentration of the free (and active) drug without any marked change in total serum concentration. However, displacement interactions may rarely be clinically important because of the rapid attainment of a new steady state. Some highly bound precipitant drugs also have enzyme-inhibiting properties; therefore, the mechanism for the interaction is not clear (eg, warfarin and sulfamethoxazole-trimethoprim).

Receptor Binding – Binding sites other than albumin are occasionally important in drug interactions. For example, quinidine displaces digoxin from binding sites in skeletal muscle, increasing the serum concentration of digoxin (quinidine also alters the renal excretion of digoxin).

Displacement of drugs from their receptor sites is generally a pharmacologic effect rather than a drug interaction. Thus, a beta-blocker, such as propranolol, may displace a beta-agonist, such as terbutaline, from $beta_2$-receptors and increase the likelihood of precipitating an asthmatic attack. Beta-blockers may produce an imbalance in response to sympathomimetics, such as epinephrine. Beta-receptor blockade may result in an excessive alpha (hypertensive) response.

Altered Metabolism: To produce a systemic effect, most drugs must reach receptor sites, which means they must be able to cross the lipid plasma membranes. Therefore, most drugs must be somewhat lipid-soluble. The role of metabolism is to change these active lipid-soluble compounds to inactive water-soluble substances that can be efficiently excreted. Enzymes, many of which are concentrated in the smooth surface of the endothelium of liver cells ("hepatic microsomal enzymes"), first oxidize, demethylate, hydrolyze, etc., the drug (phase I or "asynthetic" phase). Then, large water-soluble molecules (eg, glucuronic acid, sulfate) are attached to the drug (phase II or "synthetic" phase) to form the usually inactive water-soluble metabolite.

An important group of hepatic microsomal enzymes are the "mixed function oxidases," characterized by the cytochrome P450 isoenzymes. They are responsible for the oxidation of many drugs, such as warfarin, phenytoin, quinidine, tolbutamide, and cyclosporine. These mixed-function oxidases are the enzymes most commonly reported to be "induced" by other drugs.

Based on the current classification scheme, the entire group of cytochrome P450 enzymes represents a superfamily (CYP) consisting of families designated by an Arabic or Roman numeral (eg, CYP2 or CYPII) and subfamilies designated by a capital letter (eg, CYP2D or CYPIID), according to the similarity of amino acid sequences of the encoded P450 isozyme protein. The individual gene is designated by an Arabic numeral (eg, CYP2D6 or CYPIID6). Of the CYP genes that have been identified, families CYP1, CYP2, and CYP3 appear to be involved primarily with drug metabolism; however, the specific CYP isozyme responsible for the oxidation of most drugs is unknown. A number of drugs have been identified as substrates, inhibitors, and inducers of metabolism by the CYP enzymes (see table 3).