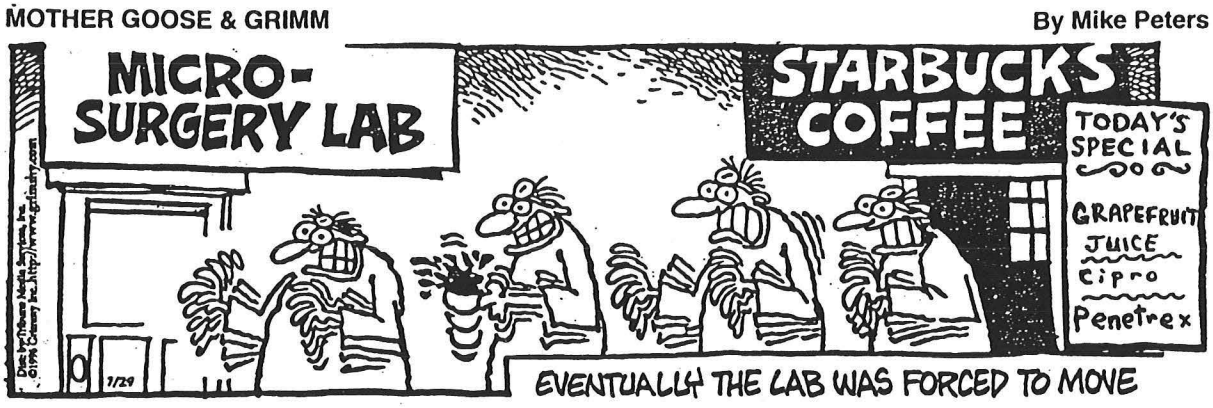
DRUG INTERACTIONS
AND
ANTI-INFECTIVE THERAPY



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I. Introduction

It is generally perceived that complications of drug therapy are a significant cause of morbidity and hospitalization or prolongation of hospital stay. However, despite the vast fund of literature and knowledge regarding drug interactions with other drugs as well as with foods and environmental chemicals that has been amassed in the last three decades, precise definition of the epidemiology and impact of drug interactions on modern medical care remains elusive. This problem is of significant practical importance, because clinicians, administrators, health insurers, and regulatory or quality assurance entities such as the Joint Commission on Accreditation of Healthcare Organizations (JCAHO) are constantly seeking to reduce the injury and expense incurred as a result of unnecessary or avoidable hospitalizations or other medical encounters. In fact, current JCAHO guidelines include criteria for active surveillance and preventive intervention for drug-drug and drug-nutrient interactions. In this review I shall discuss the recent literature on the epidemiology of drug interactions with the goal of providing clinicians with a practical perspective on the scope of the problem. Second, I shall review the best described pharmacokinetic mechanisms of drug interactions and the importance of these mechanisms in clinically significant interactions involving major categories of commonly prescribed pharmaceuticals. I shall reemphasize those interactions which involve frequently used antimicrobial drugs. Finally, because a comprehensive knowledge base in drug interactions is beyond the reasonable working memory of most people, I discuss current legal ramifications of physician and pharmacist practice that are impacted by interactions of drugs and suggest current and readily accessible text- and computer-based information systems available to clinicians for their daily use in the management of individual patients.

Drug interaction has been variously defined, but one of the more encompassing is a "measurable modification (in magnitude or duration) of the action of one drug by prior or concomitant administration of another substance (including prescription and nonprescription drugs, foods, or alcohol). The effect of the interaction can be desirable, adverse, or inconsequential." (1). There are many examples of desirable combinations of drugs in everyday use (2, 3) including cancer chemotherapy, antihypertensive regimens, treatment of peptic ulcer disease, and antibiotic combinations used for their presumed synergistic effects against bacteria or fungi. Most such desirable combinations are pharmacodynamic (see below), but many are pharmacokinetic interactions, for example penicillins plus probenecid, levodopa-carbidopa for Parkinson's disease, various antidotes for poisons or drug intoxications, and inhibition of cyclosporine metabolism so as to minimize the expense of immunosuppressive therapy in organ transplantation.

Like most the literature and texts on the subject of drug interaction, the focus on this review will be on those pharmacokinetic interactions which have adverse clinical consequences. Drug pairs will be referred to as an **object** drug or a **precipitant** drug (4) as widely used in the literature, recognizing that some sources may use alternative terminology such as "index" drug and "interacting" drug (1). The effect of the object or index drug is modified by one mechanism or another by the precipitant or interacting drug (or nutrient or other substance). Occasionally, a pair of drugs will mutually interact.

Several general characteristics of drug interactions have been posited by Hansten (5), paraphrased below, and these should be borne in mind whenever a clinician considers the literature or prescribes a potentially interacting pair:

1. There is wide interindividual variation in effects of an interacting drug pair.

2. Drug interactions may be subtle in a clinical setting, often not easily measurable, and frequently not identified by the prescriber.

3. Undesirable drug interactions may not constitute a contraindication to combined therapy but rather simply an indication for heightened physician awareness, monitoring, and possibly adjustment of dosing.

4. Most drug interactions are dose-related.

5. Adverse effects of a drug interaction are often delayed for days or weeks.

6. Although there may be similarities within a drug class, all members of the class do not necessarily interact homogeneously or predictably with other drugs.

I would add that in this age of polypharmacy in the management of patients with complex diseases, it may be difficult for the aware clinician to dissect out the culprit drug combination which has resulted in an adverse outcome. Although drug interactions are preventable, combination therapies are often unavoidable. Patients' interests are best served by clinicians who have enough working knowledge of interactions so as to be neither dangerously skeptical nor irrationally exuberant in their appreciation of drug interactions. An example of this conundrum follows:

Case Report: A 73 year old man with small cell lung cancer, hypertension, and a chronic seizure disorder recently received combination chemotherapy. On his chronic therapies of phenytoin, felodipine, folate, thiamine, aspirin, and omeprazole, a recent phenytoin level was 24 mcg/ml and the phenytoin dose was adjusted down. His course was complicated by Candida esophagitis and Clostridium difficile colitis, so fluconazole and metronidazole were added to his regimen. On this therapy he was readmitted from a nursing home to the Dallas VA Medical Center somnolent and disoriented with irregular, poorly reactive pupils but without lateralizing or other focal neurological signs. A phenytoin level was 32.7 mcg/ml, and the admitting diagnosis was phenytoin toxicity precipitated by fluconazole. Phenytoin was held and his mental status improved only to deteriorate again two days later, at which time a CT scan revealed an intracerebral hemorrhage.

Comment: This patient's admitting diagnosis of phenytoin toxicity precipitated by fluconazole therapy was rational and probably correct but may have resulted in delay in diagnosis of an intracerebral hemorrhage. Furthermore, a current textbook on drug interactions (4) lists in its index 186 drugs with which phenytoin interacts, 86 of which are judged to be "significant." Among these reported interactions this patient was taking four drugs (fluconazole, metronidazole, omeprazole, salicylates) which have been reported to increase phenytoin levels and one drug (folate) which may decrease phenytoin levels. It is thus not clear from this case whether fluconazole treatment would alone have been adequate to precipitate phenytoin toxicity, but added to other interactive drugs fluconazole may have been a significant precipitant.

In other cases, the drug interaction may be more clear-cut, but one must be cautious in judging lack of interaction when new drugs are used which may have as yet undescribed interactions:

Case Report: A 32 year old man with AIDS, peripheral neuropathy, recent onset seizure disorder, and Candida esophagitis was treated simultaneously with phenytoin, fluconazole, amitriptyline, dapsone, zidovudine, lamivudine, and indinavir. He was admitted to Parkland Memorial Hospital with ataxia, dysarthria, diplopia, decreased visual acuity, and weakness. A phenytoin level on admission was 55.6 mcg/ml. Phenytoin was discontinued and his toxic symptoms resolved.

Comment: Entry of this patient's drug list into a current computerized drug interaction program (6) disclosed seven potential interactions, but only fluconazole emerged as a precipitant drug for phenytoin toxicity. However, lamivudine and protease inhibitor drugs have been in widespread use for only a limited time, and significant interactions between them and other drugs have been described. Furthermore, recently approved drugs such as these do not yet appear in even very current textbooks of drug interactions (4). It would appear, however, that fluconazole precipitated phenytoin toxicity in this patient.

The use of readily available information resources on encountering a patient on multiple drugs may frequently disclose a potential drug interaction not already considered as a problem in this patient's evaluation and management. Furthermore, as yet undescribed interactions may occur, especially with newly available drugs. Over-the-counter drugs (7, 8) and nonprescribed and often undisclosed "alternative therapies" patients consume must also be considered (9).

II. Polypharmacy and the Epidemiology of Drug Interactions

The Boston Collaborative Drug Surveillance Program is often referred to in the drug interaction literature as a benchmark for discussion of the incidence of adverse drug effects and of drug interactions (10). It was estimated from this study that approximately 6.9% of in-hospital adverse drug effects resulted from drug interactions, almost all of which appeared to be pharmacodynamic. Wright (1) suggests, then, that in a population of hospitalized patients each receiving an average of nine drugs, adverse drug interactions occur in approximately 2%, and 0.2% of hospitalized patients overall have a serious adverse drug interaction. My review of all reported adverse drug events at Dallas VA Medical Center from 1993 through 1996, which are largely passively acquired reports, disclosed 45 clinically significant drug interactions. The object drug was warfarin in 24, phenytoin in 4, digoxin in 3, theophylline in 2, lithium in 2, quinidine in 1, and a variety of others. Thirty-nine were pharmacokinetic interactions and 6 were pharmacodynamic interactions. All cases were of toxicity rather than lack of efficacy as a result of the interaction. Because of the likely underreporting of adverse drug events (11), these figures probably significantly underestimate the actual number of drug interactions. Also, warfarin interactions are frequently detected because of routine prothrombin time monitoring, whereas pharmacodynamic interactions may go underappreciated and underreported. Separately, a review of active pharmacist interventions to avert the administration of potentially interacting pairs of drugs revealed many adverse drug events avoided before the drugs were dispensed.

Although a modest literature exists on the incidence of drug interactions as a cause for hospitalization, a recent review of this literature found poor documentation and quantitation in these studies, rendering most of them useless for identifying specific drugs or drug classes as causes for hospitalization (12). Among these studies, however, the rates of drug interactions as the putative cause of hospitalization were low, ranging from 0 to 2.8%, and cardiovascular drugs, especially digoxin, were most commonly involved. These authors could not conclude that drug interactions were a significant cause of hospitalization but suggested that methodological flaws in the available studies might mask significant underreporting of drug interactions.

A subsequent prospective study from France of 1000 geriatric patients consecutively admitted to a university hospital attempted both to identify potential interactions among drugs taken in the previous two weeks and also to determine whether drug interactions were a cause for hospitalization (13). The mean number of drugs taken per patient was 5.1 ± 2.3, and 89.4% of patients were taking two or more. Of 894 patients on two or more drugs, 538 (60.2%) were exposed to 1087 potential drug-drug interactions, the lion's share involving cardiovascular or psychotropic drugs. Of these 894 patients, 130 (14.5%) had 189 clinical adverse effects attributed to drug interactions, and for 62 patients (11.5% of the 538), the cause of hospitalization was determined to be drug interaction. Thus it would appear that in an elderly population, drug interaction may be a more common cause for hospitalization than has been demonstrable in cross sectional studies of general hospital admissions.

Polypharmacy, or the administration of multiple drugs together, appears to be the most consistent risk factor for drug interaction (14), and this is especially true for the elderly. The elderly are at risk, it is thought, because of the treatment of multiple medical conditions often encountered as people age, complicated by physiologic changes, especially diminished renal function, that accompany aging and result in altered drug pharmacokinetics (15). Several studies (12, 16), it should be noted, have not shown advancing age as an independent risk factor for drug interactions. However, what has been observed is that the elderly consume more prescription drugs than the general population (17), and 82% take non-prescription drugs, often at inappropriate doses. Polypharmacy among elderly patients is especially common among those who are hospitalized or are in long term institutional care (18). Moreover, the population of the elderly in the United States is increasing. Persons over age 65 numbered about 32 million in 1990, or 13% of the population, and this number is expected to rise to 66 million (22% of the population) by 2030. Thus the incidence of drug interactions among the elderly is likely to increase over the next several decades.

Polypharmacy and the attendant risk of drug interactions may also be problems among outpatients. In a recent prospective analysis of the medical records of 500 consecutive patients evaluated at the Dallas VA Medical Center general internal medicine clinic, the frequency of potential drug interactions was predicted using a computerized drug therapy screening program (Weideman RA, et al, 1997, unpublished). The average number of drugs prescribed per patient was 6.4, and 316 patients were predicted to have at least one interaction. A major or moderately severe interaction was predicted in 50% of patients receiving ≥ 4 drugs and in over 90% for those receiving ≥ 8 drugs. Those at highest risk for polypharmacy and predicted interaction were over 65 years old and were prescribed either captopril, cimetidine, digoxin, glipizide, or theophylline. Although this study did not attempt to detect actual drug interactions with adverse clinical effects, it points out the frequency with which many of our patients are at risk of an interaction. Besides the elderly, others at risk because of their consumption of multiple drugs include patients with AIDS (9, 19, 20) and drug abusers (1).

In their review of the problem of polypharmacy, Honig, et al (15), also point out that care by multiple medical specialists, each prescribing for the patient but not necessarily aware of the patient's other drugs or their potential for interaction, creates increased risk of drug interactions. Add to this problem the pressure applied to physicians today to prescribe medications that patients have learned about through Medline, lay publications, the Internet and on-line bulletin boards, and other mass media promotions or self-help literature (21), regulation of which has been recently relaxed by the Food and Drug Administration (the "Watch two ads and call me in the morning" syndrome). Naturally, only the expensive drugs with a large potential market are advertised. Managed care aggravates this adversarial situation so that patients now frequently

view their physician with suspicion because the economic incentives of capitated reimbursement urge physicians to withhold prescribing of costly drugs in order to preserve profits under managed care contracts.

In what is perhaps the most comprehensive continually updated text-based reference on drug interactions, Hansten and Horn review categories of underlying disease that are strongly associated with moderate-to-severe adverse drug interactions (22). These eight disease categories are risky either because of the diseases themselves or more significantly by the number and types of drugs used to treat them (Table 1).

Table 1. Diseases whose Treatment is Most Importantly Associated with Drug Interactions.

Disease	Drug Classes with Risk
Cardiovascular	Antiarrhythmics Anticoagulants Antihypertensives Calcium channel blockers Digitalis glycosides Potassium replacement
Connective tissue diseases	NSAIDs Corticosteroids Methotrexate
Gastrointestinal diseases	Antacids, Sucralfate H2-Receptor antagonists Omeprazole Cisapride
Hyperlipidemias	Binding resins Fibrates HMG Co-A reductase inhibitors
Infectious diseases	Quinolones Trimethoprim-sulfamethoxazole Macrolides Azole antifungals Rifampin HIV protease inhibitors
Psychiatric diseases	Antidepressants (TCA, SSRI, MAOI) Lithium
Respiratory diseases	Corticosteroids Theophylline
Seizure disorders	Barbiturates Carbamazepine Phenytoin

Modified from reference 22

Although it is beyond the scope of this review to discuss all possible drug interactions, certain common or particularly illustrative examples will be used to highlight those mechanisms of drug interaction that have been best described and are discussed in the following sections.

III. Mechanisms of Drug Interactions

There are numerous excellent reviews of the mechanisms of drug interactions in texts and periodical literature (1, 4, 5, 23-27). Drug interactions are segregated as **pharmacokinetic** or **pharmacodynamic** interactions, although occasionally a combination of both may be operative. Pharmacokinetic interactions involve the precipitant drug's modifying the object drug's absorption, distribution, metabolism, or excretion. By contrast, in pharmacodynamic interactions, the kinetics of the object drug are not altered but the pharmacological effect of the precipitant drug may be additive, synergistic, or antagonistic with the object drug. The most important object drugs in either type of interaction are those with a low therapeutic index, including:

Oral anticoagulants	**Digoxin**
Anticonvulsants	**Lithium carbonate**
Antiarrhythmics	**Antineoplastic drugs**
Oral hypoglycemics	**Immunosuppressive drugs**
Theophylline	**Psychotropic drugs**

Examples of interactions by different mechanisms and in different categories will focus on those interacting pairs of drugs which are given a significance rating of **1 (major severity)** or **2 (moderate severity)** with established, probable, or suspected documentation of significance according the current edition of *Drug Interaction Facts* (4). For drugs with low therapeutic index, these illustrations have been corroborated by consideration of those pairs rating 1 (avoid) or 2 (usually avoid) in the current edition of *Hansten and Horn's Drug Interactions Analysis and Management* (22). Additionally, although it does not include a significance rating, the July, 1997, edition of *The Medical Letter Drug Interaction Program* (6) has been used as a supplemental computerized reference because it is concise, current, user-friendly, and available for sale at a modest price. They all attribute the mechanism(s) of interaction if known. Each of these sources includes adequate references to primary literature so that the interested user can obtain more detailed information.

A. Pharmacokinetic Interactions

1. *Altered bioavailability of orally administered drugs*

Absorption of orally administered drugs may be impaired or enhanced as a result of drug interactions. Gastric emptying rate, gastric pH, the presence or absence of food, alteration of intestinal microbial flora, and pharmaceutical interactions in the intestinal lumen each may influence the bioavailability of certain drugs.

Drugs which alter the rate of **gastric emptying** modify the rate but ultimately not the extent of absorption of drugs. **Anticholinergics**, **opiates**, and **food** slow gastric emptying and may delay the time to peak level (Tmax) and reduce the peak concentration (Cmax) of many drugs nonspecifically, while not usually significantly reducing the area under the plasma drug concentration curve (AUC). Conversely, prokinetic drugs such as **erythromycin**, **cisapride**, or **metoclopramide** speed gastric emptying and delivery of drugs to the absorptive surface of the small intestine, often resulting in a shorter Tmax and a higher Cmax, again without necessarily changing the AUC significantly. By this mechanism, cisapride coadministration speeds to a minor degree the absorption of histamine H_2 receptor antagonists and benzodiazepines.

Metoclopramide significantly increases absorption of cyclosporine and to a lesser extent levodopa and ethanol. The absorption of drugs as tablets which are slow to dissolve, including some preparations of digoxin, may be impaired by coadministration of prokinetic drugs, but these effects are not generally clinically important.

Gastric pH may be altered by foods as well as various antacid drugs. Therapy with sodium biocarbonate decreases the bioavailability of tetracyclines but this effect may be more a result of urine alkalinization, which promotes excretion of tetracyclines, than of raising the gastric pH. Since **ketoconazole** and **itraconazole** rely for their solubility and absorption on an acidic gastric pH, antacids, histamine H_2 antagonists, and proton pump inhibitors will significantly diminish their absorption, but sucralfate has a less significant effect. A recently released liquid formulation of itraconazole may circumvent this interaction. The absorption of fluconazole is not modified by changes in gastric pH or coadministration of these antacid drugs. Neutral gastric pH may enhance the bioavailability of **cyclosporine**, which can result in toxicity (4). Other effects of antacids are discussed below.

The oral administration of some **broad spectrum antibiotics** such as penicillins and tetracyclines may suppress the growth of upper intestinal microbial flora which normally hydrolyze oral contraceptive steroid conjugates. This antimicrobial effect reduces the enterohepatic circulation of oral contraceptives and has been reported in association with unplanned pregnancy. However, this result is a rare complication of therapy with low dose oral contraceptives (28). More important is the observation that in about 10% of people who take **digoxin**, as much as 40% of the dose is converted by upper intestinal bacteria (Eubacterium lentum and perhaps others) to inactive digoxin reduction products. The growth of those bacteria can be inhibited by oral antibiotics, which results in greater bioavailability of pharmacologically active digoxin (29). Coadministration of oral **neomycin**, **erythromycin**, or **tetracyclines** has resulted in digitalis toxicity, an effect which may persist for months following cessation of the antibiotics (4). Oral nonabsorbable antibiotics can reduce the absorption of **methotrexate** by up to 50% (30).

The most frequent clinically important **intraluminal drug interactions** in the gut that alter drug bioavailability are those in which the object drug forms a nonabsorbable complex with another drug or substance by either chelation, adsorption, or ion-exchange (Table 2). This phenomenon is used to therapeutic advantage in the use of activated charcoal in the management of acute poisonings and of sodium polystyrene sulfonate (Kayexalate®) for hyperkalemia. However, an undesirable and often unanticipated adverse interaction occurs when either divalent or trivalent cationic (Ca, Mg, Al) **antacids**, **sucralfate** (sucrose aluminum sulfonate), or maybe kaolin-pectin are coadministered with certain antibiotics including **tetracyclines**, **fluoroquinolones**, and perhaps clindamycin (31). An insoluble chelate is formed, resulting in marked reduction in absorption of the antibiotic (4, 32). Milk and yogurt, which contain calcium, may result the same interaction, so coadministration of these antibiotics with dairy products or calcium tablets should be avoided. Similarly, fluoroquinolones and tetracyclines will chelate with other commonly consumed cations such as **iron**, **zinc**, and **bismuth**, all of which are readily accessible in over-the-counter products such as vitamins and antidiarrheals (e.g. Pepto Bismol®). By a similar mechanism **penicillamine** absorption is reduced as much as 66% by coadministration with antacids

or iron supplements (30). Calcium or magnesium antacids complex with **sodium polystyrene sulfonate**, reducing its capacity to bind potassium and allowing reabsorption from the gut of bicarbonate, which can result in metabolic alkalosis.

Table 2. Drugs whose Bioavailability is Significantly Decreased by Complexation Interactions in the Gut.

Precipitant Drug	Object Drug
Calcium/magnesium/aluminum antacids Iron, zinc, bismuth salts Sucralfate Calcium (milk, yogurt)	Tetracyclines Fluoroquinolones Clindamycin? Sodium polystyrene sulfonate
Cholestyramine Colestipol	Digoxin Warfarin Corticosteroids

The bile acid sequestrant anion exchange binding resins **cholestyramine** and **colestipol**, in addition to their beneficial effects in the treatment of hypercholesterolemia, will also bind weakly acidic drugs in the gut lumen, rendering those drugs unavailable for absorption and in some cases interrupting their enterohepatic circulation. This interaction is most important for the object drugs **digoxin**, **warfarin**, and some **corticosteroids** and has been used to advantage in treating digitalis toxicity. A lesser effect occurs with thiazide diuretics and gemfibrozil. These interactions with cationic antacids and ion-exchange resins can be easily avoided by timing administration of these agents and object drugs at widely separate times of day.

2. ***Displacement from plasma protein binding sites***

It is well known that most drugs to various degrees are reversibly bound to plasma proteins, mainly albumin or α1-acid glycoproteins. Albumin, the more abundant protein, binds both acidic and basic drugs, but α1-acid glycoprotein mostly binds basic drugs. For drugs that are highly protein bound, the measured total drug concentration in the plasma will rise or fall with the concentration of its binding protein. This observation can be clinically relevant to therapeutic drug monitoring in conditions of hypoalbuminemia or when the level of α1-acid glycoprotein, an acute phase reactant, rises during an illness (33). It is also a seldom proven axiom of pharmacology that only the free or unbound fraction of drug in the circulation is available to attach to tissue binding sites and exert a pharmacologic effect. Commingling of two drugs with high affinity for the same protein binding site results in competitive displacement of the drug with less affinity. Historically, teaching in clinical pharmacology included emphasis of displacement from protein binding of one drug by another as a significant cause of adverse drug interactions. It is now known that such displacement interactions may occur but that redistribution and excretion of the object drug quickly occurs and the effects of the transient rise in unbound concentration of the object drug are seldom clinically significant (34). A meaningful effect could occur if the object drug has a small volume of distribution, a low therapeutic index, and a rapid onset of action relative to its plasma concentration (1). Others would add that the mechanisms of metabolism and excretion of the free drug and the flexibility of these elimination systems to respond quickly to a rapid transient rise in free drug concentration are key factors in whether a protein binding displacement reaction will be clinically important (5, 35).

Drugs that are highly bound to albumin include oral anticoagulants, oral hypoglycemics, and nonsteroidal antiinflammation drugs. The synthetic opioids (e.g. fentanyl, methadone), some antiarrhythmic drugs (e.g. lidocaine, disopyramide), and tricyclic antidepressants are highly bound to α1-acid glycoprotein. Some β-blockers bind to both (35). It is argued on the basis of pharmacokinetic models that a select few drugs, usually given intravenously in an acute care monitored setting, may be subject to clinically meaningful protein binding displacement reactions when a competitively bound precipitant drug is suddenly administered (35). These drugs include alfentanil, buprenorphine, fentanyl, hydralazine, lidocaine, midazolam (Versed®), and verapamil. However, reference to *Drug Interaction Facts* (4) and to *The Medical Letter Drug Interaction Program* (6) reveals no clinical reports of significant interactions with these drugs that could be attributable to protein binding displacement. Amiodarone, propafenone, quinidine, or verapamil in combination with digoxin can result in elevated digoxin levels and digitalis toxicity, which may in part result from displacement of digoxin from protein or tissue binding sites. However, in each instance multiple mechanisms seem to be operative, including changes in volume of distribution and of renal and non-renal clearance of digoxin. Indeed, all current sources consulted for this review minimize the role of protein binding displacement as a significant cause of adverse drug interactions, favoring alterations in biotransformation and excretion of the object drug as the most important pharmacokinetic mechanisms of drug interaction.

3. ***Enzymatic biotransformation: the cytochrome P450 system***

Biotransformation of drugs and other xenobiotic substances refers to the enzymatic modification of a compound to one which is more easily excreted either by the liver or kidney. This ordinarily is a detoxification process by which a nonpolar compound is first oxidized or otherwise chemically altered, rendering it more polar. A second phase of biotransformation which may occur is conjugation of the oxidized drug by either glucuronidation, acetylation, or sulfation. These metabolic products are polar, more water soluble, and more easily excreted. Biotransformation processes can have harmful effects when the metabolite is more toxic than the parent compound - e.g. acetaminophen, isoniazid.

The first oxidative phase of drug biotransformation is generally carried out by one or more of a series of microsomal enzymes called the **cytochrome P450**, or mixed-function oxidase, system, which resides as membrane bound enzymes in the smooth endoplasmic reticulum. These are heme-containing enzymes whose name derives from their absorbance maximum at or near 450 nm under controlled laboratory conditions. Well described cytochrome P450 enzymes, now numbering more than 30, are found in highest concentration in the liver and, in the case of certain subfamilies, in the intestinal mucosa and other organs. Some P450 enzyme families function in metabolism of foreign substances including drugs, toxins, and carcinogens but others in the oxidation of normal endogenous steroids, fatty acids, and other compounds. Many of these enzymes are versatile in their substrate specificity, commonly able to metabolize xenobiotics or environmental substances seemingly novel to the system.

The P450 system is a "superfamily" of genes encoding isoenzymes which can be subgrouped according to their amino acid sequence homology, substrate specificity, catalytic activity, and inactivation by specific antibodies *in vitro*. The ability to group these enzymes at a molecular level has allowed a classification schema which is now

universally accepted and has supplanted earlier trivial names for individual enzymes (36, 37). All enzymes (the corresponding genes are denoted identically but in italics) are designated CYP followed by an Arabic numeral which refers to the particular family of proteins sharing at least 40% amino acid sequence homology. At least twelve families have been described in humans, of which those numbered CYP1, 2, and 3 constitute 70% of the P450 enzyme in human liver and account for almost all of the most significant oxidative biotransformation of drugs as yet known (26). Subfamilies, denoted by a capital letter, share at least 55% amino acid homology. This letter is followed in the nomenclature by another Arabic numeral which identifies the individual enzyme (e.g. CYP1A2).

Different subfamilies and isoenzymes in the P450 system have restricted substrate specificity whereas others metabolize a large variety of drugs. Those enzymes with the broadest substrate specificity are the ones involved in the largest number of drug interactions. Furthermore, there are genetic polymorphisms and ethnic differences within human populations for certain CYP subfamilies but not others, which will be discussed below.

The most important feature of cytochrome P450 enzymes that renders them significant in drug interactions is their susceptibility to **inhibition** by precipitant drugs which may or may not also be substrates for the enzymes. This inhibition may result promptly in decreased metabolism of object drugs, resulting in their accumulation and perhaps toxicity. Furthermore, some P450 subfamilies on extended exposure to certain drugs or other substances, may be **induced** to a higher rate of enzyme synthesis, resulting in accelerated metabolism of object drugs which diminishes their pharmacologic effects. The pharmacological results of inhibition or induction of P450 enzymes are summarized in Table 3.

Table 3. Pharmacologic Effects of Inhibition or Induction of P450 Enzymes on Object Drugs.

Effect	**Inhibition**	**Induction**
Hepatic metabolism	↓	↑
Object parent drug Cmax, AUC	↑	↓
Elimination half-life	↑	↓
Effects of parent drug*	↑	↓
Effects of active metabolites	↓	↑

*if metabolites are pharmacologically inactive

Both inhibitors and inducers of P450 enzymes exhibit isoenzyme selectivity which will be discussed in relation to the isoenzyme subfamilies and object drugs for which they are important. Before these discussions it may be useful to list those drugs that are involved most frequently in P450 inhibition or induction so that physicians will think to review the rest of the patient's list of medications in order to discover and avoid potential adverse interactions before prescribing them. These precipitant drugs are summarized in Table 4.

Table 4. Most Important Inhibitors and Inducers of P450 Enzymes.

Inhibitors		**Inducers**
Amiodarone	Propranolol	Barbiturates
Azole antifungals	Sulfonamides	Carbamazepine
Cimetidine	Trimethoprim	Dexamethasone
Ciprofloxacin/enoxacin	Protease inhibitors	Ethanol (chronic)
Diltiazem	Quinidine	Omeprazole
Haloperidol	SSRIs*	Phenytoin
Macrolides	Verapamil	Rifampin/rifabutin
Metronidazole		

*SSRIs = selective serotonin reuptake inhibitors

Because of the different features of CYP450 subfamilies with regard to substrate specificity, inhibition, inducibility, and genetic polymorphism, they are best discussed by subfamily rather than as a group. Appreciation of these differences among subfamilies will allow the clinician to make rational prescribing decisions to avoid adverse drug interactions.

Many drugs are actually racemic mixtures of **stereoisomers**, and sometimes the pharmacologic and clinical effects of the two enantiomers differ. Not as much is known about the biotransformation of stereoisomers as would be useful, but it has been found that certain P450 isoenzymes are stereoselective and that drug interactions involving these enzymes are as well. This literature has been comprehensively reviewed by Gibaldi (38) and examples are cited in other reference sources (4). Several frequently prescribed drugs with a low therapeutic index may be involved in stereoselective drug interactions. **Warfarin** is a racemic mixture of equal amounts of R and S enantiomers, but the S enantiomer is three to six times more potent an anticoagulant. Biotransformation of R- and S-warfarin is stereoselective: S-warfarin is metabolized by CYP2C9, while R-warfarin is hydroxylated by CYP1A2. Cimetidine, but not other histamine H_2 antagonists, has been clearly implicated in prolongation of prothrombin time and bleeding in warfarin-treated patients (4, 7). Several studies have shown that cimetidine selectively inhibits P450 oxidation of only the less potent R-warfarin (4), which accumulates and in turn is a potent inhibitor of S-warfarin hydroxylation (enantiomer - enantiomer interaction) (38, 39). Other perhaps less clinically significant stereoselective pharmacokinetic drug interactions have also been described (38).

a. ***Cytochrome P450 subfamilies and their role in drug interactions***

Among the families of P450 enzymes, certain families or subfamilies are most involved in drug metabolism and thus are conspicuously represented as intermediaries of adverse drug interactions. These isoenzyme groups are **CYP1A2**, the **CYP2C** subfamily, **CYP2D6**, and the CYP3A subfamily (principally **CYP3A4**). The pharmacogenetics, substrate specificity, inhibition characteristics, and inducibility of each of these sets of isoenzymes are sufficiently distinguishable as to warrant separate discussion of each. For each group of isoenzymes, tables will detail most of the known pharmacokinetically important object drugs and precipitant drugs or substances, but the text will concentrate on those interactions which are most clinically important. Detailed tables from a selection of reviews and references on this topic vary in their inclusiveness, and I have attempted to amalgamate these for completeness. The reader is referred to

these and other sources for access to primary literature (23, 24, 26, 27, 38, 40). *It must be remembered that there is substantial interindividual variation in P450 subfamily content, so that it is difficult to predict that a given patient will or will not suffer an adverse event for many of the described interactions.*

b. *CYP1A2*

CYP1A2 metabolizes the methylxanthines caffeine and theophylline as well as other structurally unrelated drugs, and alternative enzymatic pathways for biotransformation are frequently available which diminishes the risk of an adverse clinical event. This enzyme may also have a role in biotransformation of procarcinogens. It accounts for approximately 15% of liver P450 content and may be genetically polymorphic, its concentration and activity varying among individuals or population groups.

Table 5. Drug Interactions involving CYP1A2.

Precipitant Drugs		**Object Drugs**	
Inhibitor	**Inducer**		
Amiodarone	Lansoprazole	Acetaminophen	**Tacrine**
Enoxacin	Omeprazole	Amiodarone	Testosterone
Cimetidine	Phenobarbital	**Caffeine**	Theophylline
Ciprofloxacin	Phenytoin	Cimetidine	Tricyclics:
Erythromycin	Rifabutin	**Clozapine**	Amitriptyline
Fluvoxamine	Rifampin	Cyclobenzaprine	Clomipramine
Methoxsalen	Ritonavir	Estradiol	Imipramine
Mexiletine		Fluvoxamine	Verapamil
Mibafradil		Haloperidol	**R-warfarin**
Ticlopidine		Propranolol	
Grapefruit	Cigarette smoke		
	Charbroiled meat		
	Broccoli		
	Brussels sprouts		

CYP1A2 is inducible by environmental factors including polycyclic aromatic hydrocarbons in cigarette smoke and charcoal broiled meat as well as by some vegetables such as broccoli and brussels sprouts. As a result of induction of CYP1A2 by cigarette smoke, smokers typically require higher doses of theophylline to maintain therapeutic levels, and they have fewer problems with theophylline toxicity except when they stop smoking "cold-turkey" (as during hospitalization) (41). Similarly, smokers taking tacrine have remarkably accelerated metabolism of tacrine and may require higher doses (41).

The object drugs of documented clinical importance in interaction involving CYP1A2 are **theophylline**, **R-warfarin,** and **clozapine**, and to a lesser degree **tacrine** and **caffeine**. Fluoroquinolone antibiotics, especially **enoxacin** and **ciprofloxacin** inhibit theophylline metabolism which can result in theophylline toxicity. Less well documented but significant similar interactions have occurred between theophylline and histamine H_2 antagonists, diltiazem, macrolide antibiotics, mexiletine, and ticlopidine, but many of these drugs are inhibitors of

P450 enzymes other than CYP1A2, so the mechanisms remain incompletely defined. Both **phenytoin** and **rifampin** induce CYP1A2 and have resulted in subtherapeutic theophylline levels (4).

Amiodarone nonselectively inhibits P450 metabolism of both R- and S-**warfarin**, and significant prolongation of prothrombin time and bleeding have been reported. It is recommended to reduce the dose of warfarin by 50% during amiodarone therapy and possibly for weeks or months following its discontinuation (4).

Ciprofloxacin and enoxacin significantly inhibit **caffeine** metabolism, and patients on these antibiotics should be cautioned accordingly. Tricyclic antidepressants are metabolized by several P450 enzymes, and serious interactions with tricyclics selectively involving CYP1A2 have not been described (42).

c. ***CYP2C subfamily (CYP2C9 and CYP2C19)***

The CYP2C subfamily of cytochrome P450 is a group of isoenzymes which are compositionally closely related but have in recent years been distinguishable based on their substrate specificities. Several object drugs exhibit isoenzyme substrate specificity (e.g. S-warfarin, tolbutamide) whereas others on the list (Table 6) can enter alternative metabolic pathways. This subfamily is generally segregated into CYP2C8, 9, 10 and CYP2C19 although other enzymes have been found. Among the 2C8, 9, 10 isoenzymes, we have the most information about CYP2C9, so this isoenzyme will be discussed as representative of that cluster. In recent years, CYP2C19 has emerged as an isoenzyme with genetics and interactions distinguishable from CYP2C9, but CYP2C19 appears to be of more interest and relevance to pharmacokineticists than clinicians. Thus, although clinical interactions have been reported among many drug pairs with affinity for this subfamily, frequent or more serious interactions are reported mostly for object drugs with a low therapeutic index, most prominently **warfarin**, **phenytoin**, and **sulfonylurea** oral hypoglycemics (4, 6), which are metabolized predominantly by CYP2C9.

Table 6. Drug Interactions involving CYP2C Subfamily.

Precipitant Drugs		Object Drugs
Inhibitor	**Inducer**	
CYP2C9		
Amiodarone	Phenobarbital (?)	Buspirone
Cimetidine	Rifabutin	Diclofenac
Disulfiram	**Rifampin**	Ibuprofen
Fluconazole		Losartan
Fluvastatin		Miconazole
Isoniazid		Naproxen
Lovastatin		**Phenytoin**
Metronidazole		Piroxicam
Miconazole		Sulfamethoxazole
Paroxetine		Tamoxifen
Sertraline		**Tolbutamide**
Sulfinpyrazone		Torsemide
Sulfaphenazole		Trimethoprim
Sulfamethoxazole		**S-warfarin**
Trimethoprim		
Zafirlukast		
CYP2C19		
Cimetidine	Rifampin	**Diazepam**
Felbamate		Hexobarbital
Fluoxetine		Imipramine
Fluvoxamine		Lansoprazole
Lansoprazole		Mephenytoin
Omeprazole		Omeprazole
Ritonavir		Pantoprazole
		Phenytoin
		Ritonavir
		R-warfarin

CYP2C9 is most prominently inhibited by **amiodarone, fluconazole, miconazole,** and **trimethoprim-sulfamethoxazole**. It is inducible by rifampin and to a lesser degree by rifabutin or barbiturates.

The S- enantiomer of **warfarin** is principally metabolized by CYP2C9, whereas the less biologically active R-warfarin is oxidized by any of several isoenzymes including CYP1A2 (discussed above), CYP2C19, and CYP3A4. Wells, et al, reviewed the extensive literature on drug and nutrient interactions with warfarin and concluded that there were strong data to support that warfarin's anticoagulant effect was potentiated by any of sixteen drugs, all of which channel through the P450 system: **erythromycin, fluconazole, isoniazid, metronidazole, miconazole, trimethoprim-sulfamethoxazole, amiodarone, clofibrate, propafenone, propranolol, sulfinpyrazone, phenylbutazone, piroxicam, ethanol** (with liver disease), **cimetidine, and omeprazole** (43). Nine of these drugs are known substrates and/or inhibitors of CYP2C9 (38, 40, 44). Omeprazole inhibits R-warfarin metabolism by CYP2C19 (45). Substances that diminish warfarin anticoagulation by various mechanisms, but several of which are known inducers of various P450 isoenzymes, include **griseofulvin, rifampin, nafcillin, barbiturates, carbamazepine, chlordiazepoxide, cholestyramine, sucralfate, avocado, and foods with high content of vitamin K** (43).

Phenytoin toxicity or subtherapeutic plasma concentrations with breakthrough seizures can result from pharmacokinetic drug interactions at CYP2C9. Although some of phenytoin's metabolism is by CYP2C19, drug interactions mediated through this enzyme appear to be less clinically significant (44). Drugs commonly prescribed in the United States that inhibit phenytoin metabolism by CYP2C9 which can result in toxic elevation of phenytoin are **amiodarone**, **disulfiram**, **fluconazole**, **isoniazid**, **metronidazole** and **trimethoprim-sulfamethoxazole** (4, 44). Phenytoin toxicity can result also from CYP2C19 interactions with cimetidine, diazepam, felbamate, fluoxetine, imipramine, or omeprazole, but in general these latter interactions are better described as pharmacokinetic effects with less commonly serious clinical implications (4). Coadministration of **folate** with phenytoin has resulted in subtherapeutic phenytoin levels in some patients, but the mechanism is not clear (4).

The metabolism of **tolbutamide** is almost entirely by CYP2C9, and indeed tolbutamide is sometimes used as an *in vivo* probe for the activity of this isoenzyme. Although a number of pharmacokinetic interactions with sulfonylurea hypoglycemics have been published, few studies document a major frequency or severity of clinical interactions. Possible exceptions to this generalization are **sulfinpyrazone** and **trimethoprim-sulfamethoxazole** or other long acting sulfonamides, which inhibit CYP2C9 and have been associated infrequently with serious hypoglycemia when coadministered with sulfonylureas. Again, **rifampin**, by its induction of CYP2C9 and metabolism of sulfonylureas, may result in inadequate control of hyperglycemia (4, 6).

CYP2C19 has a minor role in the biotransformation of a number of object drugs (Table 6). **Rifampin** induces CYP2C19 but other drugs do not. Historically, it was known by the trivial name mephenytoin hydroxylase, and S-mephenytoin remains an *in vivo* probe for CYP2C19 in clinical pharmacology studies. CYP2C19 is of great interest because it is genetically polymorphic, with studies showing a bimodal distribution of "extensive metabolizers" (EM) and "poor metabolizers" (PM) within human populations (26, 45, 46). PMs may either lack the enzymes or have mutant genes that differ from those of EMs by as little as a single base pair (26). The frequency of PM phenotype in American and European whites is 3-5%, African-American 19%, Africans 8%, Japanese 18%, and Chinese 15-17% (26, 46-49). Persons with PM phenotype for CYP2C19 will metabolize drugs with specificity for that isoenzyme slowly or by alternative pathways. In some cases CYP2C19 in EMs can be made to function like that of PMs by administration of precipitant drugs that inhibit CYP2C19.

The role of this isoenzyme in drug interactions with warfarin and phenytoin has been discussed. Interactions with **diazepam** metabolism have received attention, however, because of its value as a probe for CYP2C19 and because of the frequent coadministration of such commonly prescribed drugs as cimetidine (which is available over-the-counter), proton pump inhibitors, and certain selective serotonin reuptake inhibitors.

Despite these valuable genetic and pharmacokinetic findings, relatively few clinically important drug interactions have been described for CYP2C19. Survey of *Drug Interaction Facts* (4) and *The Medical Letter Drug Interaction Program*

(6) for diazepam interactions with described inhibitors of CYP2C19 yields no drug with more than minor clinical significance in pharmacokinetic inhibition of diazepam metabolism. If there is question of a diazepam interaction, use of benzodiazepines which are metabolized by glucuronidation (lorazepam, oxazepam, temazepam) should be safe alternatives (50). Similarly, inhibitory drug interaction with CYP2C19, which is a secondary metabolic pathway for phenytoin, is regarded as a minor risk for phenytoin toxicity (44). Until more studies are available, clinicians need maintain only cautious awareness of the possibility of interactions involving this enzyme.

d. ***CYP2D6***

One of the most extensively studied P450 isoenzymes is CYP2D6, which was identified following the observation that there was genetic polymorphism in the metabolism of the drugs debrisoquine and sparteine. In recent years debrisoquine and dextromethorphan remain commonly-used probes for CYP2D6 phenotype in studies of the pharmacokinetics and pharmacogenetics of drug biotransformation. CYP2D6 has been identified as the key enzyme in the metabolism of a large number of drugs which principally affect the central nervous system and cardiovascular system. The object drugs whose therapeutic index would suggest the possibility of significant interactions are **tricyclic antidepressants**, **encainide**, **flecainide**, and **beta blockers**. Amiodarone is more significant as an inhibitor than an object drug of CYP2D6. The enzyme is inhibitable by several drugs but has not as yet been found to be inducible (Table 7).

Genetic polymorphism for CYP2D6 is evidenced by the demonstration of a bimodal distribution of its phenotype in populations. These phenotypes, as with CYP2C19, have been designated extensive metabolizer (EM) and poor metabolizer (PM). The genetics is more complex than that which is known for CYP2C19 and may involve any of several different mutations (26). PMs lack or have very low CYP2D6 activity, whereas EMs are homozygous or heterozygous for the autosomal dominant wild type allele and exhibit full 2D6 activity. PM phenotype is found in about 8% of U.S. whites, 2-4% of African-Americans, but rarely in Asians (51). CYP2D6 is found in liver as well as other organs including brain.

Table 7. Drug Interactions involving CYP2D6.

Precipitant Drug	Object Drug
Antiarrhythmics	*Antiarrhythmics, β blockers*
Amiodarone	Acebutolol
Propafenone	Amiodarone
Quinidine	Carvedilol
	Encainide
	Flecainide
	Labetalol
	Metoprolol
	Propranolol (±)
	Timolol
Psychoactive drugs, analgesics	*Psychoactive drugs, analgesics*
Cocaine	**Amitriptyline**
Fluoxetine	Amphetamines
Fluphenazine	Bupropion
Fluvoxamine (±)	Chlorpromazine
Haloperidol	**Clomipramine**
Methadone	Clozapine
Paroxetine	**Codeine**
Sertraline (±)	**Desipramine**
Thioridazine	Fluoxetine
Venlafaxine	Fluvoxamine (±)
	Haloperidol (±)
	Hydrocodone
	Imipramine
	Nortriptyline
	Oxycodone
	Paroxetine
	Perphenazine
	Propoxyphene
	Risperidone
	Thioridazine
	Tramadol
	Trazodone
	Venlafaxine
Other	*Other*
Cimetidine	Chloroquine (±)
Chlorpheniramine	Debrisoquine
Ritonavir	Dexfenfluramine
	Dextromethorphan
	Mexiletine
	Primaquine (±)
	Sparteine

Inhibition of CYP2D6 can reduce the enzymatic activity of an EM to that of a PM with clear pharmacokinetic results. However, despite the large number of drugs metabolized wholly or in part by CYP2D6, it is surprisingly uncommon to find published reports of clinically severe pharmacokinetic interactions, though they certainly occur. (4, 46). **Quinidine**, but not its stereoisomer quinine, binds to and inhibits CYP2D6 but is not a substrate for the enzyme (38). Quinidine is nevertheless among the most commonly reported precipitant drugs interacting with this enzyme. In most cases, though, except with the beta blockers **metoprolol** and **timolol**, quinidine seems not to cause severe adverse clinical outcomes through CYP2D6 interactions.

Other potent inhibitors of CYP2D6 are haloperidol (though not metabolized), fluphenazine, thioridazine, and the SSRIs with the exception of fluvoxamine and sertraline, which, like tricyclics, are only weak inhibitors (46).

Survey of *The Medical Letter Drug Interaction Program* (6) and *Drug Interaction Facts* (4) entering all major object drugs for this enzyme discovered that for **tricyclic depressants** the only moderately severe CYP2D6 interactions have been reported with **cimetidine** and **fluoxetine**. Although fluoxetine and tricyclics may be used safely together, doses of tricyclics should be reduced 75% during and for weeks following cessation of fluoxetine therapy (4). Clinically less significant interactions have occurred between tricyclics and haloperidol, labetalol, propoxyphene, phenothiazines, propafenone, quinidine, fluvoxamine, paroxetine, or sertraline. Similarly, apparently minor inhibitory interactions raising levels of

encainide and flecainide have been precipitated by amiodarone, cimetidine, and quinidine. **Ritonavir** inhibits CYP2D6, and combined therapy with several CYP2D6 substrate drugs is contraindicated according to the manufacturer's package insert, but serious interactions involving ritonavir inhibition of this enzyme have not been reported.

There are significant CYP2D6 interactions involving **beta blockers** as object drugs, precipitated by **amiodarone**, **cimetidine**, **phenothiazines**, **propafenone**, **quinidine (EMs)**, and **fluoxetine** (4, 6). Even topically applied beta blockers can be hazardous when combined with a potent CYP2D6 inhibitor. Edeki, et al, studied the effect of a subtherapeutic oral dose of quinidine on the pharmacokinetics of topically applied timolol as might commonly be used in the treatment of glaucoma. Subjects were known EMs or PMs for CYP2D6. Prior administration of quinidine to EMs resulted in a sustained increase in plasma timolol concentration and a significant reduction in exercise-induced heart rate (51). Therefore, it may be important to know the CYP2D6 phenotype of a patient before administering known inhibitors or substrates for this enzyme, but this testing is not yet clinically available. This study also points out the potency of some topically applied drugs which can be absorbed across mucosal surfaces and result in substantial systemic effects.

One metabolic pathway of **codeine** is O-demethylation to morphine, which is catalyzed by CYP2D6. It is thought that this biotransformation is the mechanism by which codeine functions as an analgesic, and a similar pathway may be important for oxycodone and hydrocodone as well. Persons who are PM for CYP2D6 may derive no hypoalgesic effect from codeine because of absence of this pathway, and EMs may be rendered unaffected by codeine therapy by coadministration of CYP2D6 inhibitors such as **quinidine** (52). *In vitro*, CYP2D6 conversion of codeine to morphine can also be inhibited by haloperidol, phenothiazines, and tricyclic antidepressants (53). These studies suggest that in patients treated with drugs which are substrates or inhibitors of CYP2D6, alternatives to codeine, oxycodone, or hydrocodone may be necessary for the treatment of mild to moderate pain.

e. ***CYP3A4***

Of all the P450 enzymes as yet described, the one in most abundance and of broadest substrate specificity for drug biotransformation and interactions is CYP3A4, once known as nifedipine oxidase. This isoenzyme is very closely related compositionally to CYP3A3 and CYP3A5, and CYP3A5 has an overlapping but less broad range of substrates. CYP3A3 and CYP3A4 are catalytically nearly identical, so CYP3A4 will be discussed as representative of this subfamily. CYP3A4 is most expressed in liver and small bowel mucosa, though it has also been found in certain tumor tissue (54). In liver, it accounts for approximately 30% of the total P450 content, and about 70% of that in gut wall (26). Because of its expression in intestinal mucosa and liver, CYP3A4 is strategically located to have a major role in presystemic metabolism of many orally administered drugs and other xenobiotics. It is not genetically polymorphic, but there can be manyfold interindividual variation in CYP3A4 content of human liver (55), a finding which may account for the wide differences in individual susceptibility to adverse interactions involving this isoenzyme (56).

Multiple substrates may bind CYP3A4 simultaneously, and inhibition and induction of this enzyme are prominent phenomena which correlate with the drug interactions which it mediates. There has not as yet been identified an ideal *in vivo* probe for CYP3A4 activity and interaction, but candidate substrates include erythromycin, dapsone, midazolam, cortisol, nifedipine, and dextromethorphan (also metabolized by CYP2D6) (26, 56). A convenient and useful *in vivo* measure of CYP3A4 catalytic activity has been developed which measures the $^{14}CO_2$ exhaled after an intravenous dose of [^{14}C -N- methyl]-erythromycin (57). This test can reflect in studies of human subjects the pharmacokinetic effects of inhibitors or inducers of CYP3A4. Cytochrome P450 enzymes and their inhibition can also be studied *in vitro* using microsomal preparations of liver samples, immunoinhibition, and genetically engineered enzymes (56).

The broad object drug specificity as well as the large number of inhibiting and inducing drugs that have been described for CYP3A4 are detailed in Table 8. The most consistently important inducers of CYP3A4 are carbamazepine, barbiturates, phenytoin, and rifampin. As in previous tables, those drugs or substances which figure most prominently in well described clinically significant drug interactions appear in the table in bold type.

Table 8. Drug Interactions involving CYP3A4.

Precipitant Drugs		**Object Drugs**		
Inhibitor	**Inducer**			
Amiodarone	**Carbamazepine**	Alfentanil	Finasteride	Propafenone
Cimetidine	Dexamethasone	Alprazolam	Fluconazole	**Quinidine**
Ciprofloxacin	Macrolides	Amiodarone	**Hydrocortisone**	Rifabutin
Clarithromycin	**Phenobarbital**	**Astemizole**	Indinavir	Ritonavir
Danazol	**Phenytoin**	Atorvastatin	Itraconazole	Salmeterol
Diltiazem	Rifabutin	Azithromycin	Ketoconazole	**Saquinavir**
Erythromycin	**Rifampin**	Bepridil	Lidocaine	Tacrolimus
Fluconazole (±)	Troglitazone	**Carbamazepine**	Loratadine	Tamoxifen
Fluoxetine		**Cisapride**	Lovastatin	Terbinafine
Fluvoxamine		Clarithromycin	Meperidine	**Terfenadine**
Indinavir		Cyclobenzaprine	**Methylprednisolone**	Testosterone
Itraconazole		**Cyclosporine**	Miconazole	**Triazolam**
Ketoconazole		Dapsone	**Midazolam**	Trimethoprim
Lovastatin		Dexfenfluramine	Nefazodone	Tricyclics
Mibefradil		Diazepam	Nicardipine	Troleandomycin
Nefazodone		Diltiazem	**Nifedipine**	Valproate
Nelfinavir		Ergot alkaloids	Ondansetron	Verapamil
Quinidine		Erythromycin	Paclitaxel	Vinblastine
Ritonavir		Estradiol	Pimozide	Vindesine
Sertraline		Etoposide	**Prednisolone**	R-warfarin
Troleandomycin		**Felodipine**	**Prednisone**	Zolpidem
Verapamil		Fenfluramine	Progesterone	
Zafirlukast				
Grapefruit				

As with discussion of the other P450 subfamilies, this review considers all object drugs with a low therapeutic index and an interaction severity score of 1 (major) or 2 (moderate) for drug pairs according to *Drug Interaction Facts* (4), in each instance corroborated by *The Medical Letter Drug Interaction Program* (6). In this way I hope to highlight those potential interactions of which clinicians should

be most aware. In the case of those object drugs for which the precipitant drugs include antimicrobials, further discussion will follow in the section that deals with antiinfective therapy and drug interactions.

(1) *Potassium channel inhibitors.* Various congenital and acquired long-QT syndromes have been described whose molecular mechanisms appear to be defects in either the slow or fast myocardial potassium channels (58). These patients are at risk of torsades de pointes polymorphic ventricular tachycardia and other arrhythmias. It is now known that the fast potassium channel is inhibited by certain antiarrhythmic drugs which can cause acquired long-QT syndrome. These drugs include quinidine, procainamide, disopyramide, sotalol, bretylium, and amiodarone. Several other drugs which are not used as antiarrhythmics nonetheless inhibit these same fast potassium channels and can be proarrhythmic: the nonsedating antihistamines astemizole and terfenadine, cisapride, bepridil, haloperidol, phenothiazines, ketoconazole, probucol, tricyclics, and pentamidine (27, 50, 58).

CYP3A4 is the principal enzyme which metabolizes quinidine, astemizole, terfenadine, and cisapride. Coadministration of any of these drugs with CYP3A4 inhibiting drugs may, by causing accumulation of the parent compound, result in prolonged QTc interval and risk of life-threatening arrhythmia. This interaction has been most clinically important with **terfenadine** (Seldane®) (59) and less commonly with **astemizole** (Hismanal®), and the precipitant drugs associated with the most clinical reports have been **ketoconazole**, **itraconazole**, and occasionally certain macrolide antibiotics, specifically **erythromycin**, **clarithromycin**, and **troleandomycin** (4, 6, 59-62). **Fluoxetine**, **fluvoxamine**, **nefazodone**, and **HIV-1 protease inhibitors** are also contraindicated with terfenadine or astemizole, though the support for this recommendation is only inferential (50, 56). Loratadine (Claritin ®) and cetirizine (Zyrtec®) are newer antihistamines which are not associated with these adverse interactions. More recently fexofenadine (Allegra®), which is a metabolite of terfenadine, has been approved by FDA as a safe alternative to terfenadine (63), and terfenadine is being withdrawn from the U.S. market (64).

Quinidine has been successfully used in combination with **amiodarone** to manage complicated arrhythmias, but pharmacokinetic studies demonstrate a rise in quinidine levels with this combination which has caused fatal torsades de pointes (4). Other inhibitors of CYP3A4 such as cimetidine, diltiazem, ketoconazole, and erythromycin may cause more modest accumulation of quinidine and are not so far reported as major precipitants of quinidine toxicity by this mechanism (4, 6). Quinidine toxicity precipitated by ritonavir or other HIV protease inhibitors has not been reported, but coadministration of ritonavir and quinidine is preemptively contraindicated because of ritonavir's strong inhibition of CYP3A4 (50).

Cisapride can prolong the QTc interval, is metabolized by CYP3A4, and can accumulate during concurrent therapy with CYP3A4 inhibitors. Although there are no published reports, data on file with the manufacturer include arrhythmias and fatalities associated with coadministration of

fluconazole, itraconazole, ketoconazole, miconazole, erythromycin, clarithromycin and **troleandomycin** (6). Cisapride is also contraindicated in combination with **SSRIs** and **HIV-1 protease inhibitors** (50). Clinically unimportant elevations of cisapride concentration occur when it is given with cimetidine (4).

(2) *Immunosuppressive drugs.* Significant drug interactions result from inhibition or induction of CYP3A4 which is principally responsible for the metabolism of cyclosporine, tacrolimus, and corticosteroids (4, 6, 65). The most important interactions involve these compounds as object drugs, although in some pairwise combinations they may be inhibitor or inducer precipitant drugs.

Significant elevations of **cyclosporine** levels, often with attendant toxicity, have been documented with coadministration of CYP3A4 inhibitors **amiodarone**; azole antifungals (especially **ketoconazole** and **itraconazole**); **diltiazem, verapamil,** and **nicardipine** (but not other dihydropyridine calcium channel blockers); macrolide antibiotics **erythromycin, clarithromycin,** and **troleandomycin** (but not azithromycin or dirithromycin); and high dose **methylprednisolone** (4, 6, 65). In some cases, however, use of diltiazem or verapamil have been nephroprotective in combination with cyclosporine. There is established evidence that CYP3A4 inducers **rifampin, phenytoin, carbamazepine,** and **barbiturates** decrease bioavailability and reduce cyclosporine levels sometimes dramatically (4, 6, 65), but valproate appears to be safe. Long-acting **sulfonamides** and perhaps **trimethoprim** in two small series of transplant patients resulted in either significant drop of cyclosporine levels or deterioration of renal function (4, 65). Coadministration of cyclosporine with HMGCoA reductase inhibitors **lovastatin** or **simvastatin** has been reported in cases of myositis and rhabdomyolysis, but fluvastatin and pravastatin have not been associated with this possible interaction (6). There is scant evidence for clinically significant interaction of cyclosporine with other CYP3A4 substrates such as quinidine, nefazodone, SSRIs, or HIV-1 protease inhibitors. Neither have fluoroquinolones been shown to change cyclosporine pharmacokinetics consistently or significantly, although there may be a pharmacodynamic interaction with ciprofloxacin or norfloxacin (case reports of rise in creatinine) (4, 6).

Tacrolimus may be metabolized by any of several P450 isoenzymes, but its principal pathway is through CYP3A4 (65). *In vitro* inhibition of tacrolimus metabolism has been demonstrated for such well characterized CYP3A4 inhibitors/substrates as diltiazem, erythromycin, fluconazole, nifedipine, prednisolone, and cyclosporine. Case reports have been few, but elevated tacrolimus levels have been described in combined therapy with **erythromycin, clarithromycin, clotrimazole, fluconazole,** and **danazol** (4, 6, 65). **Rifampin**, but not other inducers of P450 enzymes, has been reported to cause reduced tacrolimus levels and is best avoided (6, 66). No other significant tacrolimus interactions have been reported.

Several inhibitors and inducers of CYP3A4 have predictable effects on the metabolism of **corticosteroids**. Ketoconazole in high doses inhibits cortisol synthesis, but it also inhibits metabolism of methylprednisolone by CYP3A4, doubling its AUC resulting in enhanced clinical effects. Similarly, cyclosporine inhibits metabolism of prednisolone, and erythromycin and troleandomycin inhibit oxidation of methylprednisolone (4, 6). Barbiturates, carbamazepine, phenytoin, and rifampin effectively induce CYP3A4 and its metabolism of corticosteroids and fludrocortisone. There have not been reports of other interactions with corticosteroid therapy by other CYP3A4 substrates (4, 6).

(3) *Carbamazepine*. CYP3A4 has been identified as the principal metabolizing enzyme for **carbamazepine** by several different techniques (44). The most significant inhibiting interactions are those in which the precipitant drug is **erythromycin**, **clarithromycin**, or **troleandomycin**, but azithromycin and dirithromycin appear not to interact. Other drugs that have been convincingly demonstrated to precipitate carbamazepine toxicity through CYP3A4 are **cimetidine**, **diltiazem**, **verapamil**, **fluoxetine**, **fluvoxamine**, and **danazol**. Reports on interactions with tricyclic antidepressants are conflicting, and carbamazepine toxicity associated with isoniazid (CYP2C9) and propoxyphene (CYP2D6) probably result from rarely significant interactions through other enzymes (4, 6, 44). **Barbiturates** and **phenytoin** induce carbamazepine metabolism, and although there are no reports of **rifampin** as a clinically significant inducer, it is reasonable to infer that it is.

(4) *Calcium channel blockers*. **Diltiazem**, **verapamil**, and the dihydropyridine calcium channel blockers **nifedipine** or **felodipine** (and others) are metabolized by CYP3A4, and patients taking them are subject to modest accumulation and toxicity of these drugs if they concurrently take **cimetidine** but not other histamine H_2 antagonists. There are case reports of similar interactions due to the CYP3A4 inhibiting effects of **fluoxetine** but this interaction must be rare (4, 6). Perhaps more important interactions with calcium channel blockers involve induction of CYP3A4 by **barbiturates**, **carbamazepine**, **phenytoin**, and **rifampin**, but again the published evidence generally consists of single case reports or small studies of healthy subjects (4, 6). There are no published studies as yet describing interactions with **bepridil** as an object drug, but this calcium channel blocker can cause QTc prolongation, so there is theoretical risk if it is coadministered with a potent CYP3A4 inhibitor. There is no other significant literature on interaction of calcium channel blockers with inhibitors or inducers of CYP3A4. The special case of **grapefruit juice** is discussed below.

(5) *Psychotropic drugs*. CYP3A4 is the most important P450 enzyme in the metabolism of various psychotropic drugs though it shares specificity for some substrate drugs (tricyclic antidepressants, benzodiazepines, SSRIs) with CYP1A2, CYP2C19, and CYP2D6. Precipitant drugs such as cimetidine, benzodiazepines, and SSRIs share with tricyclic antidepressants a broad isoenzyme specificity and thus are most commonly associated with

P450 inhibiting interactions involving the tricyclics. These interactions are pharmacokinetically demonstrated but not usually clinically severe because secondary pathways are generally effective (4, 6, 46).

Midazolam (Versed®), **triazolam** (Halcion®), and **alprazolam** (Xanax®) are predominantly metabolized by CYP3A4, and reports of benzodiazepine interactions with inhibitors of this enzyme are almost entirely confined to these three drugs. Furthermore, interactions with midazolam are much more significant for orally administered midazolam, a dosage form not available in the U.S. Modest pharmacokinetic interactions, some associated with clinical symptoms of CNS depression, have been reported for midazolam or triazolam in combination with **itraconazole, ketoconazole, cimetidine, diltiazem, verapamil, erythromycin, clarithromycin, troleandomycin, nefazodone, fluoxetine**, and **fluvoxamine**. **Ritonavir** is contraindicated with these and other benzodiazepines metabolized by oxidation, but lorazepam, oxazepam, and temazepam, which are glucuronidated, are safe (50). As precipitant drugs, the SSRI antidepressants fluoxetine, fluvoxamine, paroxetine, and sertraline all inhibit CYP3A4 but are much less potent in this effect than other drugs such as ketoconazole (56). Nonetheless, some authors recommend caution in combining SSRI therapy with terfenadine, astemizole, carbamazepine, triazolam, alprazolam, or midazolam (46). Inducers of CYP3A4 have minimal effects on dosing of most benzodiazepines (4).

(6) *Antineoplastic drugs*. Several antineoplastic drugs are metabolized by CYP3A4 and thus might be subject to pharmacokinetic interaction with inhibitors or inducers of this isoenzyme. The drugs so far identified as wholly or in part subject to CYP3A4 biotransformation are doxorubicin, paclitaxel, cyclophosphamide, ifosfamide, epipodophyllotoxins, tamoxifen, and vinca alkaloids (54). Search of *Drug Interaction Facts* (4) and *The Medical Letter Drug Interaction Program* (6) turned up no significant clinical reports of adverse antineoplastic drug interactions which could be attributable to cytochrome P450 enzymes. Although the clinical relevance of P450 interactions involving these object drugs is not yet known, P450 interactions may in the future be useful in designing combination chemotherapy for a variety of tumors.

f. ***Grapefruit***

Quite by chance, Bailey, et al., discovered that grapefruit juice is a potent inhibitor of CYP3A4 (67). They were studying the pharmacokinetic interactions of ethanol with felodipine and used grapefruit juice as the vehicle for both ethanol and the placebo. Administration of grapefruit juice resulted in a bioavailability of **felodipine** of 284% of that when felodipine was given with water, and other data suggested inhibition of presystemic elimination. **Nifedipine** bioavailability was enhanced as well but not as dramatically as felodipine. The interaction did not occur with orange juice (67). Subsequent studies have demonstrated substantial inhibition of metabolism of other dihydropyridine calcium channel antagonists **nimodipine** (68), nitrendipine and especially **nisoldipine** (406% mean increase in Cmax, range 107-836%) (69). The magnitude of the interaction with felodipine metabolism was similar to that caused by erythromycin (70).

The metabolism of other well known substrates of CYP3A4 is also inhibited, with resultant substantial increases in Cmax and AUC, including oral **midazolam** (71), **triazolam** (72), and **ethinyl estradiol** (73). The kinetics of intravenously administered midazolam was not affected, suggesting that inhibition of CYP3A4 in gut wall was the principal site of action of the precipitant component of grapefruit juice (71).

Grapefruit juice increased peak **cyclosporine** concentration after oral administration in renal transplant patients but did not modify the metabolism of prednisone or prednisolone (74). In another study, the Cmax, AUC, and bioavailability of oral but not intravenous cyclosporine were significantly increased by grapefruit juice (75).

Perhaps more ominous, grapefruit juice was fed to six volunteers known to be accumulators of **terfenadine** (76). On concurrent administration of multiple dose terfenadine all six had detectable concentrations of terfenadine as well as QTc prolongation. In another study of single dose terfenadine in volunteers, parent terfenadine was detectable but electrocardiographic changes did not occur (77). A sudden death has occurred in a man who took terfenadine following his customary grapefruit juice (78).

Grapefruit juice also seems to inhibit other P450 enzymes besides CYP3A4. Fuhr, et al., showed that grapefruit juice decreased the metabolism and increased the AUC of **caffeine** by 23% and prolonged its half-life by 31%, suggesting that grapefruit juice inhibits CYP1A2 (79). It also inhibits 7-hydroxylation of coumarin, which is catalyzed by CYP2A6 (80).

It has been thought that one or both of the bioflavonoids naringin or its aglycone derivative naringenin, both present in grapefruit juice and giving the juice its bitter taste, were the active components in these interactions because both inhibit CYP3A4 *in vitro* (67, 69). However, more recent preliminary studies suggest that another ingredient may be a more active inhibitor of P450 enzymes (78).

Because medications are often taken in the morning, the chance of serious adverse interactions precipitated by one's breakfast grapefruit juice seems substantial. Spence (78) has recently sounded the alarm that a broader educational campaign for news media, physicians, pharmacists, grocers, and the public is clearly warranted. Awaiting such initiatives, physicians should caution patients to avoid grapefruit or grapefruit juice if they are taking **terfenadine**, **astemizole**, **dihydropyridine calcium channel inhibitors**, **verapamil**, **cyclosporine**, **triazolam**, or **estrogens**. It may also be prudent to avoid concurrent grapefruit juice and other CYP3A4 object drugs which may have serious toxic effects (e.g. HMG CoA reductase inhibitors, bepridil, carbamazepine, cisapride, quinidine, rifabutin) until studies shed more light on this issue. Since there can be inhibition of CYP1A2, physicians should also be alert to possible clinically significant accumulation of caffeine, theophylline, and tacrine (68).

4. ***Altered renal excretion***

Decreased glomerular filtration results in accumulation of all drugs that do not have an alternative route of excretion, and to the extent that drug interactions are often dose

(concentration)-related, any cause of renal failure can predispose a patient to adverse drug interactions. Aside from this general observation, interference with renal excretion of drugs can selectively predispose to drug interaction by one of two mechanisms: competition for renal tubular secretion and altered tubular reabsorption. Some interactions such as those which involve digoxin or NSAIDs are multifaceted.

a. ***Competition for renal tubular secretion.*** The pharmacokinetics of several object drugs with a low therapeutic index are affected by competition for renal tubular secretion:

(1) **Methotrexate** is eliminated by glomerular filtration and tubular secretion. Significant competitors for excretion include **NSAIDs** (may in part be caused by decreased glomerular filtration), **probenecid**, **salicylates**, **sulfonamides**, **trimethoprim**, and rarely **penicillins**. All have been associated with methotrexate toxicity but may be dose-related in that patients on low dose methotrexate as an antirheumatic are less likely to encounter these interactions than those on high doses for antineoplastic therapy (4, 6, 22). Addition of **trimethoprim-sulfamethoxazole** to chronic methotrexate therapy has resulted in severe acute megaloblastic anemia because of the combined inhibitory effects on dihydrofolate reductase (4, 6, 81).

(2) The renal tubular secretion of **procainamide** is inhibited by coadministration of **trimethoprim**, **cimetidine**, or **quinidine**, but toxic effects of accumulated procainamide or NAPA are not reported.

(3) **Probenecid** inhibits tubular secretion of organic acids and also has some inhibitory effects on hepatic glucuronidation of drugs. It is used prophylactically to inhibit renal clearance of **cidofovir**. Probenecid, in addition to its well known pharmacologic effects as a uricosuric and as an inhibitor of renal tubular secretion of **beta lactam antibiotics**, inhibits renal elimination of **methotrexate** (see above), **ketorolac** (Toradol®), **dyphylline** (but not theophylline or aminophylline), and **thiopental**.

b. ***Altered tubular reabsorption***

(1) **Lithium carbonate** is excreted by glomerular filtration, but like sodium it can be reabsorbed. Lithium toxicity can result from interactions with **thiazide** and **loop diuretics**, **ACE inhibitors** (except perhaps enalapril), and **NSAIDs** (but apparently not aspirin), which inhibit renal excretion of lithium especially in patients who are volume depleted. The effect of NSAIDs may be multifactorial.

(2) **Potassium supplements** aggravate the well known potassium retaining effects of **spironolactone**, **amiloride**, **triamterene**, and **ACE inhibitors**. Also, **trimethoprim** can cause hyperkalemia because of a distal renal tubular effect much like amiloride, so potassium supplementation should be undertaken cautiously.

(3) **Urine alkalinizers** promote ionization of weak acids which decreases their reabsorption and promotes their excretion. This effect is used to advantage in treating **salicylate** intoxication and avoiding renal injury from high dose

sulfonamide or **methotrexate** therapy. Conversely, alkaline urine promotes reabsorption of weakly basic drugs and can result in toxicity from and prolonged elimination of **amphetamines**, **ephedrine**, **pseudoephedrine**, and **quinidine**.

(4) **Urine acidifiers**, conversely, are used to hasten excretion of **amphetamines** and other **sympathomimetic amines** and **methadone** (4, 5, 6, 27) and to treat **indinavir** crystalluria.

c. ***Complex drug interactions which involve renal mechanisms***

(1) The renal effects of **nonsteroidal antiinflammatory drugs** are various, but NSAID use causes sodium and water retention which counteracts the effects of **diuretics**, leading to loss of control of hypertension or congestive heart failure (22, 82). In the elderly, in patients with preexisting renal disease, and in those on **potassium sparing diuretics**, **beta blockers**, or **ACE inhibitors**, NSAIDs can provoke hyperkalemia. Naproxen and sulindac may be less likely than other NSAIDs to have these effects. NSAID effects on lithium excretion have been discussed and are rare (4).

(2) The interactions of **digoxin** with **amiodarone**, **propafenone**, **spironolactone**, or **quinidine** may result in digitalis toxicity. The mechanisms include decreased renal and non-renal (biliary) elimination of digoxin and decreased volume of distribution of digoxin. The interaction with quinidine is especially a risk if the patient has also been on an inducer of CYP3A4 which is then discontinued, resulting in a rise in quinidine level.

B. **Pharmacodynamic Interactions**

In pharmacodynamic drug interactions, the precipitant drug does not change the pharmacokinetics of the object drug but does modify the patient's clinical response. Pharmacodynamic interactions may be antagonistic, additive, or synergistic, and many may be predicted from knowledge of the known pharmacological effects of the individual drugs. When these interactions are additive or synergistic, the clinical effects may be apparent, but many antagonistic interactions go unrecognized and attributed to either a failure of individual drug therapy or progression of the underlying disease. These interactions in some cases should be avoided altogether but in most cases are responsive to monitoring and appropriate modification of dosing. Some pharmacodynamic interactions are intentional and beneficial, e.g., naloxone for opiate antagonism; combination antihypertensive, antineoplastic, or antimicrobial regimens. Adverse pharmacodynamic drug interactions often result in neurologic, neuromuscular, or vascular symptoms, but other effects include cardiac toxicity, bleeding diathesis, photosensitivity, and changes in blood glucose. Well known examples are the potentiation of digitalis toxicity by hypokalemia (and drugs that induce hypokalemia) and bleeding that occurs as a result of coadministration of aspirin or NSAIDs with warfarin. The diverse array of pharmacodynamic drug interactions is beyond the scope of this review. Several well described and potentially frequent of serious interactions will be summarized.

1. The monoamine oxidase inhibitors **isocarboxazid**, **phenelzine**, **tranylcypromine**, and **selegiline** block the presynaptic catabolism of dopamine, norepinephrine, and serotonin. Interactions with tyramine-containing foods or sympathomimetic drugs may result in severe hypertensive crisis, and physicians and pharmacists are obligated to

inform patients of these interactions and avoid the prescription or dispensing of interacting drugs (83, 84). Drugs that are contraindicated with MAOIs because of this and other severe adverse reactions are **bupropion**, **buspirone**, **carbamazepine**, **dexfenfluramine**, **fenfluramine**, **levodopa**, **meperidine**, **sumatriptan**, and the sympathomimetics **dopamine**, **epinephrine**, **methylphenidate**, **norepinephrine**, **phenylpropanolamine**, and **pseudoephedrine**. Although they have been used safely together, **tricyclic antidepressants** are also contraindicated with MAOIs because of many reports of fever, rigidity, seizure, confusion, coma, and death as a result of this combination (4, 50). **SSRIs** interact with MAOIs, dexfenfluramine, or fenfluramine to cause a "serotonergic syndrome" characterized by CNS irritability, rigidity, shivering, myoclonus, and altered consciousness (4, 50).

2. **Noncardioselective beta blockers** inhibit the beta adrenergic effects of **epinephrine**, and the resulting unopposed alpha adrenergic stimulation results in hypertension (22). However, the risk of this interaction is low if epinephrine is given by inhalation or in low doses combined with local anesthetics by injection. A moderate to high risk of a hypertensive reaction is associated with higher doses of epinephrine, such as might be used for extensive plastic surgery, or ophthalmic administration of epinephrine (22). Patients on nonselective beta blockers may not respond to epinephrine given systemically for anaphylaxis.

3. Several drugs or drug classes share an anticholinergic effect through muscarinic receptors and alone or in combination can result in an anticholinergic syndrome, especially in the elderly. These drugs are **quinidine**, **H_1 antihistamines**, **phenothiazines**, and **tricyclic antidepressants** (1, 25).

4. The beneficial effects of **levodopa** in Parkinson's disease can be inhibited by the dopamine antagonists **haloperidol**, **metoclopramide**, and **domperidone** (1).

5. **PUVA** - treated patients are twice as likely as controls to have UV-induced burns if they are concurrently taking photosensitizing drugs including **sulfonamides**, **tetracyclines**, **sulfonylureas**, **thiazides**, or **fluoroquinolones** (85).

IV. Anti-infectives and Drug Interactions

As has been apparent from the discussion of mechanisms of drug interactions, anti-infectives often have a prominent role in potentially serious interactions. In this section I shall consider several major antimicrobial drugs or drug classes which have been implicated in drug interactions and review not only serious interactions but also those interactions which may be more minor, infrequent, or less well documented than those in the previous section. In this way, the clinician wishing to prescribe an anti-infective drug can quickly assess current knowledge of which other drugs may be a problem if coadministered with this antimicrobial.. I shall segregate interactions according to whether the anti-infective is the object drug or the precipitant drug. With many drug pairs, the mechanism of interaction is known, but with others it is not. The principal reference sources for this review are *Drug Interaction Facts* (4) corroborated in each case by *The Medical Letter Drug Interaction Program* (6), which were searched in their entirety for interactions involving each anti-infective. Primary citations are available in these references, but where appropriate, other supporting literature is also denoted.

A. *Fluoroquinolones*

Table 9. Drug Interactions involving Fluoroquinolones (see text).

Fluoroquinolones as object drugs	
Aluminum, magnesium, calcium antacids	Iron, zinc, bismuth
Didanosine	Ranitidine
Milk, yogurt	Antineoplastic drugs
Sucralfate	Probenecid
Fluoroquinolones as precipitant drugs	
Theophylline	Mexiletine
Caffeine	Diazepam
Warfarin	Procaineamide
Phenytoin	Cyclosporine
Metoprolol	Foscarnet
Propranolol	

1. *Fluoroquinolones as object drugs.* The bioavailability of orally administered fluoroquinolones is dramatically impaired by coadministration with divalent or trivalent cations because of the formation in the upper intestine of insoluble nonabsorbable chelates. This effect is most dramatic with aluminum-, magnesium-, or calcium-containing **antacids**, **sucralfate**, **milk**, and **yogurt**, all of which can decrease the bioavailability of fluoroquinolones by as much as 90%. The buffer in **didanosine** has a similar effect on coadministered fluoroquinolones. A more modest but still significant decrease in absorption occurs on coadministration with **iron** or **zinc** supplements. Treatment failures have occurred (86). Other interactions that have been associated with decreased fluoroquinolone absorption are reported as small studies or case reports and include **ranitidine** and various **antineoplastic drugs** which damage intestinal mucosa. **Probenecid**, in a small study of healthy volunteers, decreased renal excretion of ciprofloxacin.

2. *Fluoroquinolones as precipitant drugs.* The clearly most important interaction is the ability of **enoxacin**, **ciprofloxacin**, and, to a lesser extent, **norfloxacin** to inhibit the metabolism of **theophylline** by CYP1A2, resulting in theophylline accumulation and toxicity. No corresponding change occurs in fluoroquinolone pharmacokinetics. Newer fluoroquinolones ofloxacin, levofloxacin, sparfloxacin, and temafloxacin do not inhibit CYP1A2 and do not interact with theophylline (87). Coadministration of **cimetidine** may aggravate the fluoroquinolone-theophylline interaction. A case of seizures induced by a combination of ciprofloxacin and theophylline in a patient with a therapeutic theophylline level suggests a pharmacodynamic interaction as well (88). The mechanism may be additive antagonism of γ-aminobutyric acid (89).

   The effect of fluoroquinolones on warfarin anticoagulation is modest, rarely reported, and subject to large interindividual variation (90). Enhanced anticoagulation has been seen with ciprofloxacin, norfloxacin, or ofloxacin but not enoxacin, levofloxacin, sparfloxacin, or temafloxacin. Controlled studies have demonstrated no effect of fluoroquinolones on warfarin anticoagulation.

   Enoxacin as well as **ciprofloxacin** inhibit CYP1A2 metabolism of **caffeine**, prolonging its t½ 4-5 fold and increasing its AUC and Cmax. Norfloxacin modestly inhibits caffeine metabolism. Again, this effect has not been found with ofloxacin, levofloxacin, lomefloxacin, sparfloxacin, or temafloxacin.

There are case reports of decreased phenytoin levels when fluoroquinolones were coadministered, but controlled studies show no effect on phenytoin elimination. There is one report in which ciprofloxacin increased the AUC of metoprolol and propranolol by 50%. Other small studies show modest similar effects on mexiletine, diazepam, and procainamide.

Possible pharmacodynamic interactions involving fluoroquinolones include not only the case of theophylline toxicity already mentioned but also case reports of cyclosporine (nephrotoxicity) and foscarnet (seizures) interactions. Cytochrome P450 metabolism of cyclosporine may also be inhibited by norfloxacin (91).

B. *Trimethoprim-Sulfamethoxazole*

These antimicrobials are available separately as trimethoprim (Trimpex®) and sulfamethoxazole (Gantanol®) or as a fixed combination (Bactrim®, Septra®) often referred to as co-trimoxazole. Their mechanism of action is sequential inhibition of folic acid synthesis in microorganisms, an effect which in part is operative in some adverse drug interactions in the host. These antimicrobials also have interactive effects with other drugs mediated by alterations of hepatic biotransformation, competitive renal excretion, and pharmacodynamic synergism or antagonism. In all significant interactions, they are precipitant drugs.

Table 10. Drug Interactions involving Trimethoprim-Sulfamethoxazole (see text).

Trimethoprim as an object drug	
Amantadine	
Dapsone	
Trimethoprim-sulfamethoxazole as precipitant drugs	
Potassium-sparing diuretics	Methotrexate
Potassium supplements	Cyclosporine
Thiazide diuretics	Azathioprine
Amantadine	Phenytoin
Dapsone	Rifampin
Digoxin	Loperamide
Procaineamide	Oral contraceptives
Zidovudine	Pimozide
Warfarin	6-Mercaptopurine

1. *Trimethoprim as an object drug.* Coadministration of trimethoprim with amantadine or dapsone results in accumulation of both trimethoprim and the other drug. There are no reports of adverse effects of the higher level of trimethoprim.

2. *Trimethoprim-sulfamethoxazole as precipitant drugs.*

   Several interactions can be attributed to trimethoprim and others to sulfamethoxazole, but in many instances the combination is implicated, and the effects of the two are not distinguishable. Trimethoprim is a weak cation and competes for renal tubular secretion with several drugs. It also inhibits sodium channels in the distal tubule much like pentamidine and the potassium-sparing diuretics amiloride and triamterene. Trimethoprim used alone can cause hyperkalemia, which has been reported in the elderly and in patients with AIDS. This effect may be aggravated by addition of trimethoprim to therapy with **potassium-sparing diuretics** or **potassium supplements** including salt substitutes (92). Combined treatment with trimethoprim

and **thiazide** diuretics has resulted in severe hyponatremia (93, 94). Inhibition by trimethoprim of renal excretion of **amantadine, dapsone, digoxin, methotrexate, procaineamide**, or **zidovudine** has been reported in cases of toxicity of these object drugs. With the dapsone interaction in AIDS patients, methemoglobinemia occurred, but there were fewer failures of dapsone therapy for Pneumocystis carinii.

Sulfa drugs including sulfisoxazole and trimethoprim-sulfamethoxazole have been significantly associated with aggravating the hypoprothrombinemia of **warfarin** therapy. The mechanism of this interaction has been elusive, however. There is evidence that a modest displacement of warfarin from plasma protein binding sites occurs, but this is unlikely to be a major mechanism. Results are conflicting from studies of circulating levels of either enantiomer of warfarin (95, 96, 97), but sulfamethoxazole may inhibit CYP2C9, the major cytochrome P450 isoenzyme responsible for biotransformation of the more potent S-warfarin (98). O'Reilly, et al, suggest that the interaction of trimethoprim-sulfamethoxazole and warfarin may be pharmacodynamic (97). Some authorities would monitor prothrombin times more frequently with combined warfarin and trimethoprim-sulfamethoxazole therapy, and others would not use these drugs together at all.

Trimethoprim-sulfamethoxazole in combination with **methotrexate** may cause bone marrow suppression by any of several mechanisms. Sulfa drugs may displace methotrexate from plasma protein binding sites resulting in transiently higher levels of unbound methotrexate. Additionally, trimethoprim competes with methotrexate for renal tubular secretion and excretion. Also, a pharmacodynamic effect of combined inhibition of dihydrofolate reductase can result in acute megaloblastic anemia when trimethoprim is added to chronic methotrexate therapy. Folinic acid has been helpful in managing some cases. This combination is sufficiently hazardous as to be avoided.

Either trimethoprim or sulfamethoxazole may dramatically diminish **cyclosporine** levels, resulting in transplant rejection. Trimethoprim may also have a pharmacodynamic effect of causing a rise in serum creatinine in patients on cyclosporine. There are case reports of leukopenia resulting from a pharmacodynamic interaction of trimethoprim and **azathioprine**.

Sulfamethoxazole or trimethoprim, presumably by inhibiting CYP2C9, can cause a modest increase in the t½ and decrease in the clearance of **phenytoin**. However, reports of clinically significant phenytoin toxicity as a result of this combination are scarce. Patients on **rifampin** therapy will have slightly higher rifampin levels if trimethoprim-sulfamethoxazole is taken (99), presumably a result of inhibition of P450 metabolism of rifampin. Coadministration with trimethoprim-sulfamethoxazole has also been reported in association with loperamide toxicity, which has been attributed to cytochrome P450 inhibition.

The effects of several drugs may be diminished when patients are also treated with trimethoprim-sulfamethoxazole, including **oral contraceptives, pimozide**, and **6-mercaptopurine**. The mechanisms of these interactions are unknown.

Finally, concurrent administration of trimethoprim-sulfamethoxazole and **thiazide** diuretics has been epidemiologically associated with thrombocytopenia (100). At particular risk for this possible interaction are elderly patients with chronic congestive heart failure, but again the mechanism is unknown.

C. *Macrolide antibiotics*

Various macrolide antibiotics have different propensities to cause adverse drug interactions in large measure because of differences in their chemical structure which modify their abilities to bind to and inhibit cytochrome P450 isoforms, especially CYP3A4. These differences allow us to classify the macrolides into three groups which correlate with their association with significant inhibitory precipitant interactions with a large number of drugs and alteration of those object drugs' pharmacokinetics (101-105). In Group 1 are **erythromycin** and **troleandomycin** which bind strongly to and inhibit CYP3A4 and are associated with the most significant interactions. In Group 2 are **clarithromycin** and a number of experimental macrolides which have intermediate binding affinity to CYP3A4. Group 3 includes **azithromycin, dirithromycin** and some other drugs not as yet approved in the U.S. Group 3 macrolides do not bind CYP3A4 and are associated with the fewest adverse interactions. Although many interactions are well documented, it is worth recalling that there can be as much as a tenfold interindividual variation in CYP3A4 activity, so significant adverse outcomes are not necessarily predictable in a given patient. There are a few interactions in which a macrolide is the precipitant drug by a mechanism other than inhibition of P450 isoenzymes, and there also are several interactions in which macrolides are object drugs.

1. *Macrolides as object drugs.* Several drugs or substances interact with macrolides to decrease their bioavailability. Ethanol decreases absorption of erythromycin ethylsuccinate, and food modestly decreases absorption of all macrolides except clarithromycin and enteric coated erythromycins. Antacids have a minor effect in decreasing bioavailability of all macrolides except azithromycin. Presystemic metabolism of Group 1 and Group 2 macrolides by CYP3A4 is inhibited by **ritonavir**, which results in higher macrolide blood levels and may be advantageous in the management of infections caused by Mycobacterium avium complex in AIDS. Cimetidine also inhibits microsomal P450 metabolism of erythromycin and has been associated with precipitating transient reversible deafness caused by high dose erythromycin (106). **Rifampin** and to a lesser degree **rifabutin** induce microsomal metabolism of a number of drugs including Group 1 and Group 2 macrolides, which may result in treatment failures with macrolide therapy.

2. *Macrolides as precipitant drugs.* A few pharmacokinetic interactions in which macrolides are the precipitant drug are sufficiently expected, well documented, or potentially life-threatening as to be considered major interactions. The object drugs include **astemizole, terfenadine, carbamazepine, cisapride, cyclosporine, digoxin, ergot alkaloids, pimozide, theophylline,** and **warfarin** (Table 11).

Table 11. Drugs with Potentially Serious Interactions with Macrolides.

Astemizole	Digoxin
Terfenadine	Ergot Alkaloids
Carbamazepine	Pimozide
Cisapride	Theophylline
Cyclosporine	Warfarin

   a. The nonsedating H_1 antihistamines **astemizole** and **terfenadine**, both metabolized by CYP3A4, will accumulate if a potent inhibitor of CYP3A4 is coadministered. These antihistamines cause a dose-dependent prolongation of QTc and rarely torsades de pointes. Group 1 and Group 2 (but not Group 3) macrolides, by

inhibiting CYP3A4, have been associated with approximately 10% of the reported cases of terfenadine cardiotoxicity (107-110). This adverse effect is rare but best avoided. A similar interaction occurs between macrolides and loratadine (Claritin®) but loratadine is not cardiotoxic.

b. Inhibition by Group 1 and 2 macrolides of CYP3A4 metabolism of **carbamazepine** is a widely acknowledged major drug interaction which can result in carbamazepine toxicity within one to several days, documented by many case reports, case series, and controlled studies. Azithromycin and dirithromycin have not been reported with this complication, but as a rule macrolides should not be prescribed for patients on carbamazepine.

c. **Cisapride** can prolong QTc and is metabolized by CYP3A4. Although no cases have been reported of cardiotoxicity from the combination of cisapride with macrolide therapy, the manufacturer's package insert notes ventricular arrhythmias with erythromycin or clarithromycin therapy and recommends that the coprescription of Group 1 and 2 macrolides with cisapride be avoided (22).

d. Many case reports and studies have documented the ability of Group 1 and 2 macrolides to inhibit metabolism of **cyclosporine**, resulting in its accumulation and toxicity (4, 6, 111). This effect may be immediate (within hours) and occurs whether the macrolide is given orally or intravenously. There has also been a single case report of cyclosporine toxicity with concurrent azithromycin therapy, and small increases in cyclosporine levels are precipitated by dirithromycin as well. There are several case reports of elevated **tacrolimus** levels and toxicity following erythromycin therapy in organ transplant recipients (112, 113).

e. Already discussed in the section on altered gastrointestinal absorption is the ability of oral antibiotics including erythromycin to inhibit intraluminal metabolism of **digoxin** by Eubacterium lentum, resulting in increased bioavailability and toxicity of digoxin. The same phenomenon probably occurs with concurrent clarithromycin therapy but has not been reported with Group 3 macrolides (114).

f. **Ergot alkaloids** are rarely prescribed any more, but there are many reports that a severe interaction can occur if there is concurrent therapy with the Group 1 macrolides troleandomycin or erythromycin. Acute ergotism occurs, even with low dose ergot, manifest by severe vasospasm, which has resulted in amputation and other permanent disability.

g. **Pimozide** (Orap®), used for treatment of Tourette's disorder, causes prolongation of QTc and is metabolized by CYP3A4. Two sudden deaths have occurred during concurrent treatment with clarithromycin, so FDA has ruled that all macrolides are contraindicated with pimozide (115).

h. Group 1 and 2 macrolides inhibit microsomal metabolism of **theophylline** to a variable degree, and reports of this possible interaction are conflicting. Theophylline also decreases the bioavailability of orally administered erythromycin. This interaction should be regarded as potentially a significant cause of theophylline toxicity but is unusual and unpredictable. Again, Group 3 macrolides have not been associated with theophylline toxicity.

i. Erythromycin has been reported to cause excessive hypoprothrombinemia and serious bleeding in several patients on stable **warfarin** dosing. Pharmacokinetic studies show a modest effect of erythromycin in decreasing warfarin clearance, presumably by inhibition of cytochrome P450 isoforms important in warfarin metabolism.

A variety of other drugs metabolized by CYP3A4 can accumulate to toxic levels if coadministered with Group 1, and in some cases Group 2 macrolides. Since these interactions share a common mechanism but are either rare or have not been reported as causes of major drug toxicity, they are grouped and listed in Table 12.

Table 12. Other Drugs with Possible Interactions with Group 1 Macrolides.

Alfentanil	Fluoxetine	Quinidine
Bromocriptine	Glyburide	Rifabutin
Clozapine	Lovastatin	Triazolam
Colchicine	Methylprednisolone	Valproate
Disopyramide	Midazolam	
Felodipine	Phenytoin	

Group 1 macrolides and also dirithromycin have been reported in single cases and a small study to decrease the effects of oral contraceptives. Troleandomycin has also caused cholestatic jaundice in women concurrently taking oral contraceptives.

Lastly, clarithromycin seems to alter the absorption of zidovudine, but the results of two studies are conflicting. The clinical significance of this possible interaction is unknown.

D. *Azole Antifungals*

The mechanisms of interaction involving azole antifungals, specifically **ketoconazole**, **itraconazole**, and **fluconazole**, either as object or precipitant drugs are either alterations of solubility and absorption of the azole or modified P450 biotransformation by either the azole or the other drug in the interacting pair. Some P450-mediated interactions modify both drugs in the pair and are summarized in Tables 13 and 14.

Table 13. Interactions in which Azole Antifungals are Object Drugs. Azole levels are *decreased.*

Ketoconazole/Itraconazole	Fluconazole
Decreased absorption	
Antacids	Cimetidine (slight)
Didanosine (buffer)	
Sucralfate	
H_2 antihistamines	
Proton pump inhibitors	
Enhanced metabolism	
Rifampin	Rifampin (slight)
Rifabutin	
Phenytoin	
Isoniazid*	
Carbamazepine**	

* 3 case reports with ketoconazole

** Only reported with itraconazole

1. *Azole antifungals as object drugs.* Ketoconazole and itraconazole are soluble at acid pH but only 10% soluble at pH 6. **Antacids**, including the buffer which stabilizes didanosine, and inhibitors of gastric acid secretion including **H_2 antihistamines** and **proton pump inhibitors**, dramatically decrease the bioavailability of these two azoles. **Sucralfate** also decreases bioavailability of ketoconazole by 20%. Ketoconazole or itraconazole can be used effectively if given at least 2 hours before antacids or sucralfate. During concurrent treatment with H_2 antihistamines or proton pump inhibitors, absorption can be enhanced if ketoconazole or itraconazole is taken with a cola drink or other acidic beverage or if the new liquid formulation of itraconazole is used. In contrast to ketoconazole, the absorption of itraconazole is maximal if it is taken with a meal (116). Fluconazole does not depend on acidity for its dissolution and absorption, though its bioavailability is slightly decreased by coadministration with cimetidine.

   Rifampin and to a lesser degree rifabutin induce several P450 isoenzymes which increase the metabolism of ketoconazole and itraconazole. Ketoconazole levels have been decreased 80%, and itraconazole has been undetectable during rifampin treatment (117, 118). This interaction has resulted in antifungal treatment failures, but cryptococcal infections may still respond because of antimicrobial synergism between itraconazole and rifampin against Cryptococcus neoformans (117). Rifampin induces only a modest drop in serum levels of fluconazole. In several case reports, **isoniazid** treatment decreased concurrent ketoconazole serum concentration by as much as 80% resulting in ketoconazole treatment failure (4). The mechanism of this interaction is unknown.

   Phenytoin decreases serum concentrations of both ketoconazole and itraconazole, and **carbamazepine** decreases the serum level of itraconazole. These interactions have been associated with failure of antifungal therapy (117).

2. *Azole antifungals as precipitant drugs.* As with interactions in which azoles are object drugs, there are some similarities and some differences among the azoles in their interactions as precipitant drugs (Table 14). The significant precipitant interactions all seem to involve inhibition of cytochrome P450 enzymes, and the differences lie in the different isoenzyme specificity of fluconazole (principally CYP2C9) compared to ketoconazole and itraconazole, which inhibit CYP3A4. Large doses of fluconazole also can inhibit CYP3A4, which probably accounts for its interactions with the nonsedating antihistamines, cisapride, cyclosporine, and tacrolimus.

Table 14. Interactions in which Azole Antifungals are Precipitant Drugs.

Ketoconazole/Itraconazole		Fluconazole
Potentially serious		
Astemizole		Astemizole
Terfenadine		Terfenadine
Cisapride		Cisapride
Cyclosporine		Cyclosporine
Methylprednisolone*		Tacrolimus
Midazolam		Phenytoin
Triazolam		Warfarin
Unusual or minor		
Digoxin**	Rifabutin**	Caffeine
Felodipine**	Simvastatin	Lovastatin
Fluoxetine**	Sulfonylureas*	Rifabutin
Indinavir*	Vincristine**	Simvastatin
Lovastatin**	Warfarin*	Tricyclics
Quinidine*	Chlordiazepoxide*	

* Reported with ketoconazole only

** Reported with itraconazole only

The most serious interactions of azole antifungals are with the nonsedating antihistamines **terfenadine** and **astemizole**. Accumulation of the cardiotoxic parent drugs resulting from CYP3A4 inhibition by the azole causes prolongation of QTc and ventricular tachyarrhythmias including torsades de pointes (59). Ketoconazole and itraconazole are the most commonly associated drugs reported with this interaction, though others, especially macrolide antibiotics, have been implicated as well (60-62, 119, 120). Fluconazole has a similar though less dramatic effect on terfenadine metabolism but can result in prolonged QTc in certain subjects on concurrent terfenadine (121). Other drugs which can accumulate in the presence of CYP3A4 inhibitors and prolong QTc have been discussed under Mechanisms of Drug Interaction. Cisapride is one such drug which is considered contraindicated with azole antifungals, as fatalities have been reported to the manufacturer as a result of this interaction (50).

Azole antifungals inhibit the CYP3A4 metabolism of **cyclosporine** and **tacrolimus**, which can result in toxicity. Ketoconazole is a more potent inhibitor of cyclosporine metabolism than are itraconazole or fluconazole, and in fact ketoconazole has been used for cyclosporine dose-sparing (122). Whereas case reports and series generally show elevated levels and decreased metabolic clearance of cyclosporine with ketoconazole, other studies, particularly of itraconazole and fluconazole, are contradictory (4, 65). Tacrolimus levels and AUC have been increased by concurrent treatment with clotrimazole or fluconazole, but fluconazole can be used safely if the tacrolimus dose is reduced (65). Ketoconazole, but not itraconazole or fluconazole decreases the clearance of methylprednisolone and perhaps prednisolone, but a consistent effect on prednisone metabolism has not been found (4, 6).

To a significant degree, the metabolism of orally-administered **midazolam** and **triazolam**, which are oxidized by CYP3A4, will be inhibited by ketoconazole or itraconazole therapy (123, 124) but less dramatically by fluconazole (125). This effect is not seen with intravenous midazolam which is the only form of this drug available in the U.S. With either drug Cmax is fourfold elevated, AUC 10-15 times control, and t½ prolonged 2-3 times, which results in excessive and prolonged sedation. If given to a

patient on ketoconazole or itraconazole neither of these drugs should be considered a short-acting benzodiazepine (4). Ketoconazole also causes a 20-30% decrease in clearance of chlordiazepoxide, which is considered clinically insignificant (4, 6).

Fluconazole, but not ketoconazole or itraconazole, increases the AUC of **phenytoin** by 75% and the serum concentration by 128%, presumably as a result of inhibition of phenytoin biotransformation by CYP2C9. There are case reports of phenytoin toxicity, exemplified by the Cases Reports in this review (4, 6).

S- warfarin is hydroxylated by CYP2C9, and **R- warfarin** is metabolized in part by CYP3A4, both reactions inhibitable by fluconazole (126). Although there has been a case report of potentiation of warfarin-induced hypoprothrombinemia by ketoconazole, there is more substantial evidence that fluconazole increases the effect of warfarin on coagulation (127). One case of aggravation of warfarin-induced hypoprothrombinemia was associated with application of miconazole oral gel, but none have been reported secondary to vaginally or cutaneously applied azoles (6).

A number of other object drugs have appeared in case reports as interacting with either ketoconazole, itraconazole, or fluconazole, resulting in toxicity of the object drug. These drugs are compiled in Table 14 (4, 6, 128, 129). Anterior uveitis caused by rifabutin has been associated occasionally with concurrent fluconazole or itraconazole therapy in AIDS patients, and theoretically ketoconazole should have the same effect. A possible interaction of ketoconazole with theophylline is of doubtful significance and is not included (6).

Object drugs whose effects may be diminished by interaction with azole antifungals are oral contraceptives (6, 130) and rifampin (4). However, there has been a total of only five case reports of contraceptive failure presumably resulting from concurrent azole therapy (6). In one case report, ketoconazole decreased the Cmax and AUC of rifampin by 50%, which was associated with failure of treatment of tuberculosis.

E. ***Rifamycins***

Rifampin and the related drug rifabutin are macrocyclic antibiotics with diverse antimicrobial effects that are useful in treatment of mycobacterial, bacterial, and some fungal infections. Rifampin inhibits hepatic assimilation of bromsulfophthalein but is also the most potent and broadly specific inducer of cytochrome P450 isoenzymes, including CYP1A2, the CYP2C subfamily, and CYP3A4. Rifabutin, whose antimicrobial value is largely limited to treatment of M. avium complex infections, is a less potent P450 inducer. Both rifampin and rifabutin may be involved in a variety of interactions either as object (Table 15) or more importantly as precipitant drugs (Table 16). In all of the significant precipitant interactions, the rifamycins induce P450 metabolism of the object drug, reducing its bioavailability, Cmax, and often t½, which sometimes results in failure of therapy with the object drug (117, 131, 132, 133).

1. *Rifamycins as object drugs*. By mechanisms that are unknown, concurrent administration of aluminum hydroxide antacids, ketoconazole, or pyrazinamide can reduce the oral bioavailability of rifampin. The other rifamycin interactions as object drugs result from decreased metabolism of the rifamycin with resultant toxicity.

Table 15. Interactions involving Rifamycins as Object Drugs.

Decreased bioavailability
Aluminum-containing antacids
Ketoconazole
Pyrazinamide
Decreased metabolism
Macrolide antibiotics (clarithromycin)
Azole antifungals
HIV-1 protease inhibitors
Delavirdine
Trimethoprim-sulfamethoxazole

Concurrent administration of rifabutin with **clarithromycin**, **fluconazole**, or **itraconazole** has resulted in high rifabutin serum levels and chronic uveitis or other therapy-limiting effects such as polyarthralgia (134-138). The HIV-1 protease inhibitors **indinavir**, **nelfinavir**, and **ritonavir**, and the non-nucleoside reverse transcriptase inhibitor **delavirdine** are potent inhibitors of CYP3A4 and other P450 isoforms (139). Theoretically, accumulation and toxicity of rifamycins could occur if they are coadministered with these antiretroviral agents. Rifampin is contraindicated with indinavir, ritonavir, and delavirdine and not recommended with saquinavir or nelfinavir. Rifabutin is contraindicated with delavirdine both because of rifabutin toxicity and induction of delavirdine metabolism. If rifabutin is to be used with protease inhibitors, the dose of rifabutin should be reduced by 50-75% or an alternative drug considered (139). Nevirapine induces cytochrome P450 enzymes and theoretically may interact with rifamycins, but clinical studies have not yet yielded firm recommendations on this combination. Trimethoprim-sulfamethoxazole, also commonly used in patients with AIDS, will raise concurrent rifampin levels (133).

2. *Rifamycins as precipitant drugs*. There is a long list of object drugs whose metabolism is induced by concurrent treatment with rifampin or rifabutin, which reduces the pharmacologic effects of the object drug. Some of these interactions are more severe or more predictably common than others, and therefore the object drugs are segregated according to severity in Table 16.

Table 16. Interactions involving Rifamycins as Precipitant Drugs.

More severe and/or common	
Corticosteroids	Phenytoin
Cyclosporine	Propranolol
Disopyramide	Quinidine
Isoniazid	Sulfonylureas
Itraconazole	Tacrolimus
Ketoconazole	Theophylline
Methadone	Tocainide
Metroprolol	Verapamil
Oral Contraceptives	Warfarin
Less severe or common	
ACE inhibitors	Fluvastatin
Acetaminophen	Haloperidol
Barbiturates	Lamotrigine
Chloramphenicol	Mexiletine
Clofibrate	Nifedipine
Dapsone	Nisoldipine
Diazepam	Progestins
Digoxin (dialysis)	Propafenone
Diltiazem	Triazolam
Doxycycline	Tricyclics
Fluconazole	Zidovudine

Major induction interactions have occurred between rifamycins and **corticosteroids**, resulting in decreased steroid effects within days and loss of clinical control in patients with Addison's disease, asthma, nephrotic syndrome, organ transplants, and giant cell arteritis (4, 6, 65). Similarly major interactions occur with **cyclosporine**, **tacrolimus**, **itraconazole**, and **warfarin**, necessitating substantially increased doses of the object drugs or alternative therapy (65, 66, 131, 132). In patients who must continue the rifamycin, when it is withdrawn at the end of therapy, there is usually a washout period of 1-3 weeks during which cytochrome P450 metabolism returns to baseline. During that time, object drug levels may rise resulting in toxicity if not adjusted closely. This has been particularly true with cyclosporine, tacrolimus, sulfonylureas, theophylline, quinidine and warfarin (4).

Rifampin interacts with **isoniazid** by inducing a secondary metabolic pathway that converts isoniazid to hydrazine which is hepatotoxic. This interaction can result in severe hepatitis in persons (especially children) who are slow acetylators of isoniazid (4).

The relatively minor interaction of rifampin with digoxin or digitoxin resulting in decreased digitalis levels has been described in patients with renal failure who depend on non-renal (hepatic) elimination of digitalis glycosides. Rifampin induces this metabolic pathway and may necessitate an increase of digoxin dose by 35-100% to maintain therapeutic levels. The dose should be decreased 50% when rifampin is discontinued (132).

F. *Antiretrovirals*

Patients with HIV-1 infection, and particularly those whose disease has advanced to AIDS, are typically prescribed multiple drugs, not only combination antiretroviral regimens employed for their presumed synergistic antiviral effects but also several antimicrobials for prophylaxis or treatment of opportunistic infections. HIV patients also often take other

medications which may interact with their antiretroviral drugs including psychotropics, antiarrhythmics, gastrointestinal drugs, and analgesics. Moreover, these patients frequently receive prescriptions from physicians of different specialty disciplines, and many take non-prescription drugs (NSAIDs, H_2 antagonists, antacids, nontraditional medicinals, vitamins, protein supplements) which may interact with one or more drugs in a prescribed regimen. The product of this polypharmacy is a multitude of possible theoretical or demonstrated pharmacokinetic or pharmacodynamic drug interactions which can in some cases enhance certain therapies but in most instances result in deleterious effects either as a result of drug toxicity or failed therapy.

Many drug interactions encountered in HIV patients involve macrolide antibiotics, azole antifungals, fluoroquinolones, trimethoprim-sulfamethoxazole, and rifamycins, which have already been discussed. This section will address only the antiretroviral drugs as object and precipitant drugs and will focus on those known or potential interactions likely to have significant clinical impact. These interactions have been the subjects of several excellent recent reviews (139-143), which are collated here with monographs on the different drug pairs in *Drug Interaction Facts* (4) and *The Medical Letter Drug Interaction Program* (6).

Antiretroviral drugs will be discussed individually as either object or precipitant drugs. Some important interactions are pharmacodynamic but most are pharmacokinetic. I shall not review synergistic or antagonistic antiviral activities of drug combinations against HIV-1.

1. *Nucleoside analogues.* The currently available nucleoside HIV-1 reverse transcriptase inhibitors are zidovudine (ZDV, AZT), didanosine (ddI), zalcitabine (ddC), stavudine (d4T), and lamivudine (3TC).

    a. **Zidovudine** is the nucleoside antiretroviral most likely to be involved in adverse drug interactions. It is the object drug in several pharmacokinetic interactions and one serious pharmacodynamic interaction (Table 17). Zidovudine is 70% glucuronidated in the liver and excreted by renal tubular secretion. Inhibition and induction interactions involve one or both of these steps.

Table 17. Interactions involving Zidovudine.

Pharmacodynamic	
Ganciclovir	
Acyclovir	
Pharmacokinetic	
↑ **Zidovudine level**	↓ **Zidovudine level**
Atovaquone	Rifampin
Fluconazole	Rifabutin
Interferon β-1b	Food
Methadone	
Probenecid	
Trimethoprim-sulfamethoxazole	
Valproate	

The most serious interaction of zidovudine is with **ganciclovir**, a pharmacodynamic effect of synergistic hematologic toxicity, which results in neutropenia in the majority of patients on higher doses of zidovudine concurrently with standard doses of ganciclovir. Although most physicians now use lower doses of zidovudine in routine care, the addition of another drug which raises zidovudine levels (Table 17) theoretically could potentiate this interaction with

ganciclovir. As a rule, zidovudine is to be avoided in patients on ganciclovir, and foscarnet is considered a lesser risk than ganciclovir to interact if zidovudine were considered necessary.

Pharmacokinetic drug interactions that cause elevated zidovudine levels result from inhibition of glucuronidation (atovaquone, fluconazole, IFN β-1b, methadone, valproate), renal excretion (trimethoprim, sulfa drugs ?), or both (probenecid). Any nephrotoxic drug can result in diminished excretion of zidovudine and toxicity. Such drugs commonly used in patients with AIDS include aminoglycosides, amphotericin B, cidofovir, foscarnet, and pentamidine (intravenous). Hepatic glucuronidation is induced by the rifamycins, and fatty meals inhibit absorption of zidovudine, either of which can result in decreased bioavailability of zidovudine and perhaps failure of antiretroviral therapy.

b. **Didanosine** requires neutral gastric pH for absorption and is eliminated by renal tubular secretion and glomerular filtration. There are some minor pharmacokinetic interactions and potentially more significant pharmacodynamic interactions involving didanosine (Table 18).

Table 18. Interactions involving Didanosine.

Pharmacodynamic		
	Cisplatin	Pentamidine
	Dapsone	Ribavirin
	Ethanol	Ritonavir
	Isoniazid	Stavudine
	Lamivudine	Vincristine
	Metronidazole	Zalcitabine
	Nitrofurantoin	
Pharmacokinetic: object drug		
↑	**Didanosine level**	↓ **Didanosine level**
	Ganciclovir	Food
	Ranitidine	Ketoconazole
Pharmacokinetic: precipitant drug		
	Dapsone	Ketoconazole
	Fluoroquinolones	Pyrimethamine
	Indinavir	Rifampin
	Itraconazole	Trimethoprim

The significant pharmacodynamically interacting drugs with didanosine are those which may cause peripheral neuropathy (cisplatin, dapsone, isoniazid, metronidazole, nitrofurantoin, ribavirin, stavudine, vincristine, zalcitabine) or pancreatitis (ethanol, lamivudine, pentamidine). A case of gout is reported in a patient concurrently on didanosine and ritonavir.

The pharmacokinetic interactions in which didanosine is the object drug are generally inconsequential, except that **food** decreases didanosine absorption 50%, so it is to be taken fasting. Didanosine is a precipitant drug in several pharmacokinetic interactions because of the buffer incorporated with the nucleoside. This buffer chelates fluoroquinolones, and the neutralization of gastric acid decreases the absorption of drugs that require a low pH for solubility (dapsone, indinavir, itraconazole, ketoconazole, pyrimethamine, rifampin, trimethoprim).

c. **Zalcitabine** is a neurotoxin and may rarely cause pancreatitis. It should be cautiously used in combination with other drugs which can cause peripheral neuropathy or pancreatitis (see above).

d. **Stavudine**, like zalcitabine and didanosine may cause peripheral neuropathy or pancreatitis, so it is to be used carefully in patients on these nucleosides or the other cautionary drugs listed above.

e. **Lamivudine** is renally excreted and causes few adverse interactions, although its use has rarely been associated with peripheral neuropathy and pancreatitis. The same drugs already discussed above are best avoided, although lamivudine is often successfully used in combination nucleoside therapies.

2. *Non-nucleoside reverse transcriptase inhibitors*. There are two non-nucleoside reverse transcriptase inhibitors marketed in the U.S.: nevirapine and delavirdine. Both are metabolized by hepatic P450 enzymes, principally CYP3A4. Nevirapine is also an inducer of CYP3A4 while delavirdine inhibits CYP3A4. Few clinically significant interactions have been described for these drugs, and recommendations on their combined use with other drugs emanate from *in vitro* testing and other data on file with their manufacturers. All potential interactions so far have been pharmacokinetic.

   a. **Nevirapine** induces CYP3A4 and may reduce the effects of coadministered **oral contraceptives** and HIV-1 **protease inhibitors**. There may be an as yet unexplained inhibition of clearance of rifampin or rifabutin which in turn induce metabolic clearance of nevirapine. Clinical evidence for a significant interaction of these drugs so far is lacking.

   b. **Delavirdine** inhibits CYP3A4, and its metabolism by the same enzyme is induced by carbamazepine, phenobarbital, phenytoin, and rifamycins. Pharmacokinetic studies show that delavirdine inhibits 75% of CYP3A4 activity as measured by the erythromycin breath test (144), which can increase the concentration of other substrates of this P450 isoform, including HIV-1 protease inhibitors (145). Drugs whose concentration and potentially toxic effects are increased by delavirdine are listed in Table 19.

Table 19. Drugs Potentiated by Delavirdine.

Alprazolam	Midazolam
Astemizole	Protease inhibitors
Cisapride	Quinidine
Clarithromycin	Rifamycins
Dapsone	Terfenadine
Dihydropyridine CCBs*	Triazolam
Ergot alkaloids	Warfarin

*Calcium channel blockers

Concurrent therapy with delavirdine and **alprazolam, astemizole, cisapride, midazolam, rifabutin, rifampin**, and **terfenadine** is contraindicated.

3. *HIV-1 protease inhibitors*

The HIV-1 protease inhibitors indinavir, nelfinavir, saquinavir, and ritonavir are all metabolized by CYP3A4, but ritonavir is also a substrate of CYP2C9 and CYP2D6. This broader isoenzyme specificity of ritonavir and its avid binding characteristics are reflected in the more significant drug interactions associated with or predicted for ritonavir. In addition to its P450 inhibitory effects, ritonavir induces glucuronyl transferase, which diminishes the effects of oral contraceptives and theophylline. Saquinavir is the least bioavailable protease inhibitor until a recent reformulation was released, and it has the least potent CYP3A4 inhibitory effects. Indinavir and nelfinavir are more potent than saquinavir but less than ritonavir. P450 interaction among protease inhibitors has led to the combined use of saquinavir and low dose ritonavir, which results in dramatically increased bioavailability (50-100x) of saquinavir without a change in adverse effects. Other similar combination protease inhibitor therapies are under investigation.

a. **Saquinavir** levels are increased by concurrent **ritonavir**, **ketoconazole**, **group 1 and 2 macrolides**, **delavirdine**, and **grapefruit juice**. Because it is a CYP3A4 inhibitor, it is not recommended for combined use with **astemizole**, **terfenadine**, **cisapride**, **ergot alkaloids**, **rifampin**, or **rifabutin**. There are as yet no reports of adverse clinical outcomes resulting from these combinations, however.

b. **Indinavir** is a substrate of and more potent inhibitor of CYP3A4 than saquinavir. Like the other protease inhibitors, its Cmax and AUC are increased by **ketoconazole** and decreased by **rifampin** or **rifabutin**. The buffer in didanosine will reduce indinavir absorption if the two are given simultaneously but not if separated by 2 hours. Because of its inhibition of CYP3A4, indinavir is not recommended for concurrent use with **astemizole**, **terfenadine**, **cisapride**, **ergot alkaloids**, **midazolam**, **rifampin**, or **triazolam**. Concurrent indinavir increases the effects of zidovudine, stavudine, clarithromycin, rifabutin, and trimethoprim which may be a factor in dosing decisions.

c. **Nelfinavir** is roughly equivalent to indinavir as a CYP3A4 inhibitor (146). Consquently, current recommendations on drugs to avoid for patients taking nelfinavir are the same as for indinavir.

d. **Ritonavir** has the highest affinity and broadest isoenzyme specificity of the current protease inhibitors. Like indinavir, its absorption is diminished by simultaneous administration of didanosine (buffer effect). By inducing glucuronyl transferase, ritonavir accelerates metabolism and elimination of **ethinyl estradiol**, **theophylline**, **sulfamethoxazole**, and **zidovudine**. However, the most significant predicted interactions involve ritonavir as an inhibitor of CYP2C9, CYP2D6, and CYP3A4. Many substrates of these enzymes with a low therapeutic index are listed by the manufacturer as contraindicated, although there are only rare published reports of actual clinically important pharmacokinetic interactions with ritonavir (6, 22). In one case report, the effect of triazolam was increased, and in another, published as an abstract, a patient had elevated rifabutin levels while on concurrent ritonavir. The concurrent drugs to be avoided in patients on ritonavir are listed in Table 20.

Table 20. Drugs to Avoid with Ritonavir.

Drug Class	Drugs
Analgesics	Meperidine, piroxicam, propoxyphene
Antiarrhythmics	Amiodarone, encainide, flecainide, propafenone, quinidine
Antibiotics	Clarithromycin, erythromycin, rifabutin*, rifampin
Antifungals	Itraconazole, ketoconazole
Antihistamines	Astemizole, terfenadine
Antihypertensives	Bepridil
Contraceptives, oral	Ethinyl estradiol
Ergot alkaloids	All
Gastrointestinal drugs	Cisapride
Hypnotics	Alprazolam, clorazepate, diazepam, estazolam, flurazepam, midazolam, triazolam, zolpidem
Psychotropics	Bupropion, carbamazepine, clozapine, pimozide

*Rifabutin may be used at a dose 150mg QOD

In addition to the drugs in Table 20, others whose metabolism is inhibited by ritonavir and should be use cautiously are fluoxetine, some beta blockers (metoprolol, propranolol, timolol), and tricyclic antidepressants. A disulfiram reaction may occur if ritonavir is given concurrently with disulfiram or metronidazole.

V. Physician Prescribing Practices, Pharmacist Intervention, and the Two-edged Sword of Computer Databases

Only 40% of currently available drugs were on the market when today's 40 year old physician was in medical school (147), so continuing education on appropriate prescribing is essential to modern medical practice. Many managed care organizations try to educate physicians on prescribing, but with the clear motive of saving money for the insurer. Pharmaceutical companies and their representatives attempt to educate physicians, too, but with the overt or indirect goal of marketing their own products. From either source, there is always risk that information will be incomplete or biased. The package inserts with drugs or their entries in *Physicians Desk Reference* are tedious to read and do not usually provide worthwhile information on drug interactions that is stratified according to incidence or severity. Furthermore, the package inserts for new drugs such as antiretrovirals sped to market through the FDA's recently accelerated approval process often fail to include recently acquired important information on drug interactions (147).

There are several text-based and computerized database references which can be useful to physicians and pharmacists in their attempts to prescribe and dispense safe combinations of drugs for patients. No single system is ideal (148). A text such as *Drug Interaction Facts* (4), which was used for this review, is useful because it is relatively inexpensive, portable, and comprehensively reviews drug pairs which have been marketed for at least a few years or have been studied extensively, but such texts lack information on new drugs. *Drug Interaction Facts* has been criticized for other methodological reasons, too (149). *Hansten and Horn's Drug*

Interactions Analysis and Management (22) is continually updated, thorough, and has a slightly more practical severity rating system than *Drug Interaction Facts*, but it has the disadvantage of its bulkiness, so it is usually unhandily stationed in the reference section of a medical library. Various computer database programs on drug interactions are commercially available to physicians, hospitals, and community pharmacies (6, 150, 151), but these vary widely in their quality of data, ease of use, and cost. For this review, for instance, *The Medical Letter Drug Interaction Program* (6) was used because it was relatively inexpensive (approximately $125), updated quarterly, and very user-friendly. It has listings for recently released drugs, but its discussions are too short; it does not stratify interactions by severity or incidence; and it was missing one well-known life-threatening interaction documented in other ready sources. These deficiencies do not seriously undermine my favoring this program for all-around value for the money for practicing physicians, but a critical comparison with other more expensive programs was not performed. Any of these sources is only as valuable as the quality and completeness of the database, which sometimes falls short of the mark (152).

The attention that has been focused in the last several years on the life-threatening interactions of terfenadine or astemizole with erythromycin or azole antifungals illustrates how difficult it is to educate physicians and pharmacists on drug interactions so as to modify prescribing and dispensing practices. Most drug interactions are not immediately life-threatening, but this one is, albeit rarely, and should have gotten people's attention. The first case report of this interaction was published in December, 1990, five years after terfenadine had been on the U.S. market (59). In June, 1990, FDA had ruled to revise the labeling of terfenadine to warn against coprescription with ketoconazole or macrolides, and in August, 1990, terfenadine's manufacturer sent a "Dear Doctor" letter to over 300,000 health professionals to advise of this change. However, concurrent prescribing continued, such that by 1992 terfenadine was the tenth most prescribed drug in the U.S.; had been prescribed cumulatively to over 100 million persons worldwide; and was related to approximately 80 cardiovascular events reported to the manufacturer (153, 154). Another "Dear Doctor" letter, an FDA press release, extension of the warnings to astemizole, and inclusion with both drugs' labelling a "black-box" contraindication warning followed in July, 1992.

Several groups have studied the impact of these major educational initiatives on concurrent prescribing and dispensing of these contraindicated drug pairs. Zechnich, et al, reviewed Oregon Medicaid prescription claims over the course of the announcements and found that concurrent use increased threefold from 1991 to 1992 (153). In half of these, prescriptions were received from different physicians, but in 97% both prescriptions were filled at the same pharmacy, 25% on the same day. It was concluded that many physicians remain unaware of this dangerous interaction but that pharmacists are strategically placed and should be essential in prospective screening to intercept these prescriptions. Since Congress in the Omnibus Budget Reconciliation Act of 1990 had required pharmacists to screen at point of sale for drug interactions, it was reasoned that more emphasis should be placed on the use of computerized drug interaction programs in pharmacies to assist in this expanding role.

Carlson, et al, reviewed drug reimbursement claims to a management firm for several HMOs to determine the rate of coprescription of terfenadine with either erythromycin or ketoconazole from 1990 to 1993 (155). They found an approximately 50% decrease in concurrent prescribing of terfenadine with erythromycin but only rarely was terfenadine prescribed with ketoconazole, in part because ketoconazole was infrequently prescribed at all. These authors had several criticisms of the passivity of governmental regulation and the ineffectiveness of the notification processes by the pharmaceutical industry. They also recommended an increased role for the pharmacist in detecting and preventing these interactions.

In a similar study, Thompson, et al, reviewed pharmacy claims to a large health insurer in New England from 1990 to 1994 and noted a decline of 84% in same-day dispensing and a 57% decline in overlapping use of erythromycin and terfenadine (154). These authors emphasized, however, that concurrent prescribing of terfenadine with macrolides and azoles continued to occur despite the publicity.

The most recent large study is that of Burkhart, et al, from FDA (156). They reviewed the computerized claim forms from 1988 through 1994 of Michigan and Ohio Medicaid as well as a large HMO database looking for coprescription of these contraindicated drug pairs. They documented that concurrent prescribing of these drugs declined sharply after 1992 but did not disappear.

In April, 1996, Cavuto, et al, published their informal study to determine whether community pharmacies were intercepting simultaneous prescriptions for erythromycin and terfenadine (157). Fifty pharmacies were presented the prescriptions, and 16 (32%) filled them without comment. Of the 50 pharmacies, 48 used computerized drug interaction programs, but 29% of these programs were judged ineffective. This study was highlighted later that summer in the featured article "Danger at the Drugstore" on drug interactions in *U.S. News and World Report* (158).

It is apparent from these studies that large scale educational efforts can modify prescribing and dispensing practices, but it is disturbing that there has been incomplete penetration of these efforts into the medical and pharmacy professions. It is thus no surprise that warnings of less well publicized or serious drug interactions go unheeded. Clearly, physicians are liable for prescribing combinations of drugs with a foreseeable probability of adverse interaction (159).

The pharmacist is increasingly the focus of recent shifts in social policy to try to prevent adverse drug reactions and interactions. In *Dooley v. Everett*, a Tennessee appellate court ruled that pharmacists have a legal duty to detect drug interactions and warn patients (160). It was pointed out in this case that computer technology gave pharmacists the tools to fulfill such a duty. More recently, in *Baker v. Arbor Drugs*, the Michigan Court of Appeals held that a retail pharmacy which voluntarily advertised its drug interaction computer program as part of a marketing effort assumed liability when adverse interactions were not prevented (83, 84). So on the one hand, pharmacists may be held liable for negligence if they fail to counsel patients, but when they use the now ubiquitous computer-based drug interactions programs, pharmacists are also responsible to use them effectively. Computer databases are more effective than individual pharmacists at detecting drug interactions (Weideman RA, et al, unpublished), but computer-based detection is inconsistently applied (148, 157).

The future promises that pharmacists will be increasingly effective at intercepting and preventing serious adverse drug interactions by using computer technology (161). Clinicians may object at times to this interventional role taken by modern pharmacists, but such prospective intervention appears to be a necessary safeguard in current and future medical practice.

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