Centers for Education &
Research on Therapeutics™

CLINICAL PHARMACOLOGY **EDUCATIONAL MODULE 1**

Preventable Adverse Drug Reactions:

A Focus on Drug Interactions

Acknowledgements

The following individuals played a critical role in this educational module by serving as authors of version 1.0:

David A. Flockhart, MD, PhD
Chief, Division of Clinical Pharmacology
Indiana University School of Medicine

Peter Honig, MD, MPH
Executive Vice President, Worldwide Regulatory Affairs & Product Safety
Merck & Co., Inc.

Sally Usdin Yasuda, MS, PharmD
Research Assistant Professor
Department of Pharmacology
Georgetown University School of Medicine

Curtis Rosebraugh, MD, MPH
Director, Office of Drug Evaluation II
U.S. Food and Drug Administration

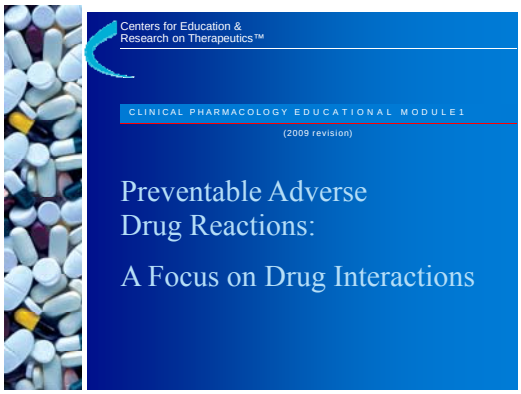
Funded by 1 U18 HS 10385-01 from Agency for Healthcare Research and Quality

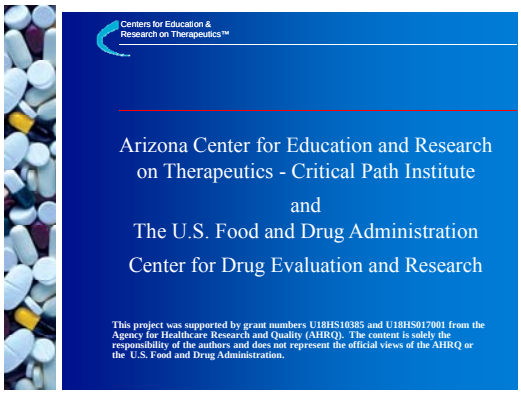
Preventable Adverse Drug Reactions: A Focus on Drug Interactions

Lecture Guide Contents

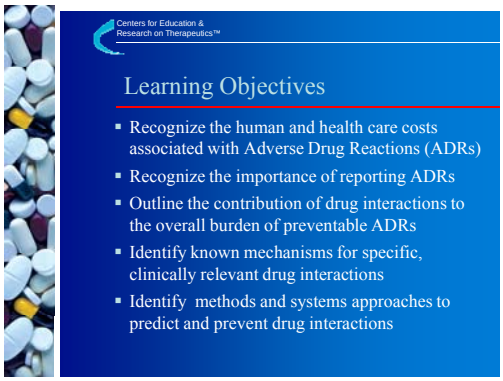
- Drug Interaction Reference Card (front pocket)
- Speaker's Notes
- Literature References
- Self-Assessment Test Questions
- Evaluation Form
- Slide Set and Speaker's Notes CD (back pocket)

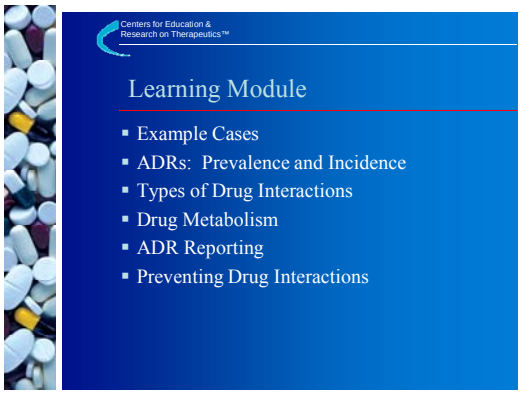
Preventable Adverse Drug Reactions: A Focus on Drug Interactions




Centers for Education &
Research on Therapeutics™
Arizona Center for Education and Research on Therapeutics - Critical Path Institute
and
The U.S. Food and Drug Administration
Center for Drug Evaluation and Research
This project was supported by grant numbers U18HS10385 and U18HS017001 from the Agency for Healthcare Research and Quality (AHRQ). The content is solely the responsibility of the authors and does not represent the official views of the AHRQ or the U.S. Food and Drug Administration.

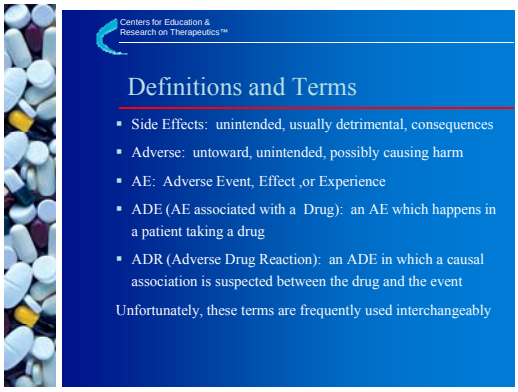
Preventable Adverse Drug Reactions: A Focus on Drug Interactions

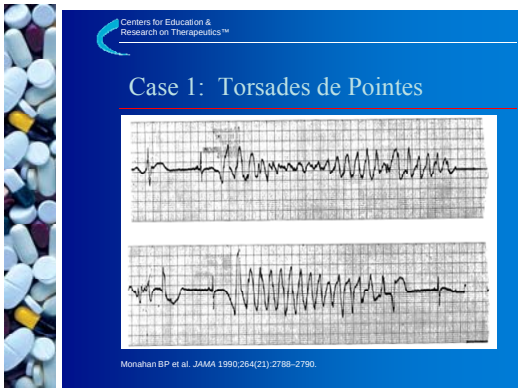




Welcome to the Adverse Drug Reaction (ADR) learning module. The module will begin with presentation of cases that highlight the potential clinical consequences of preventable drug interactions.

After reviewing the cases, we will discuss the prevalence and incidence of adverse drug reactions. We will then examine several well-recognized types of drug interactions that often result in preventable adverse reactions. This section will focus primarily on cytochrome P450-mediated drug interactions, although other types of interactions will also be discussed, as well as examples of drug-drug, drug-diet, and drug-herbal interactions. The emphasis will be on current knowledge that can help healthcare providers predict potential drug interactions. This will be followed by a discussion of ADR reporting to the FDA's MedWatch program. Finally, a stepwise systems approach to prevent ADRs due to drug interactions will be outlined.


Centers for Education & Research on Therapeutics™
Definitions and Terms
Side Effects: unintended, usually detrimental, consequences
Adverse: untoward, unintended, possibly causing harm
AE: Adverse Event, Effect ,or Experience
ADE (AE associated with a Drug): an AE which happens in a patient taking a drug
ADR (Adverse Drug Reaction): an ADE in which a causal association is suspected between the drug and the event
Unfortunately, these terms are frequently used interchangeably

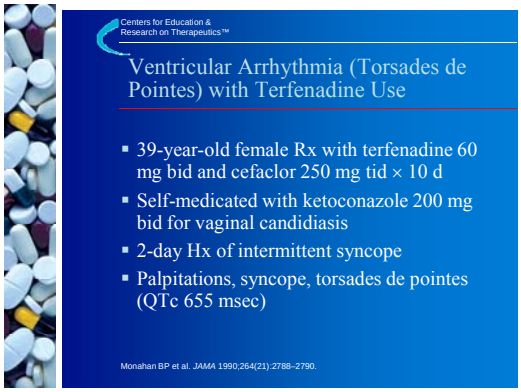


The first case we will consider is that of the potentially lethal arrhythmia, *torsades de pointes* (French for "twisting of the points"), occurring in a young woman and in association with the administration of the antihistamine terfenadine (Seldane®).[1]

This ECG is a classic example of *torsades de pointes*, and describes how the arrhythmia appears on the ECG. The ventricular complexes during this rhythm tend to show a series of "points going up" followed by "points going down," often with a narrow waist between. *Torsades de pointes* is a form of ventricular tachycardia that is most often due to medications, but can occur in patients with an inherited disorder of cardiac ion channels, i.e., the congenital long QT syndrome. Clinically, *torsades de pointes* is a syndrome in which rapid polymorphic ventricular tachycardia (very often, but not always, showing the twisting of the points pattern) occurs in the setting of prolongation of cardiac repolarization (QT interval prolongation on the ECG).

Recognition and reporting of this arrhythmia in association with terfenadine (Seldane®), astemizole (Hismanal®), cisapride (Propulsid®), grepafloxacin (Raxar®), levomethadyl (Orlaam®), cerivastatin (Baycol®) and mibefradil (Posicor®), ultimately led to these medications' removal from the regular prescription market.

1. Monahan BP, Ferguson CL, Killeavy ES, Lloyd BK, Troy J, Cantilena LR. Torsades de pointes occurring in association with terfenadine use. JAMA 1990; 264:2788-2790.



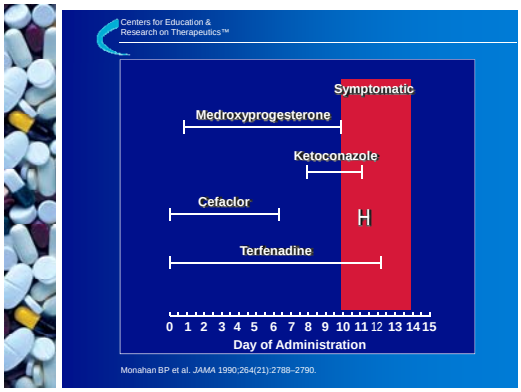
A 39-year-old female was evaluated for episodes of syncope and light-headedness that began two days prior to her hospital admission.[1] The history was consistent with possible cardiovascular causes, and the patient was admitted and placed on telemetry where the preceding rhythm strip was observed.

Ten days prior to admission, she had been prescribed terfenadine (Seldane® - an antihistamine) 60 mg twice-a-day and cefaclor (Ceclor® - a cephalosporin antibiotic) 250 mg three-times-a-day. On the eighth day of terfenadine therapy the patient began a self-medicated course of ketoconazole (Nizoral® - an azole antifungal drug) at 200 mg twice-a-day for vaginal candidiasis. She was also taking medroxyprogesterone acetate at a dosage of 2.5 mg a-day.

Upon admission to the hospital, the patient was noted to have a QTc (Bazett correction) interval of 655 milliseconds (normal is less than 440 milliseconds). During the hospitalization, the patient experienced near syncopal episodes associated with *torsades de pointes* observed on ECG telemetry.

After discontinuing the medications, the QTc interval normalized. She had no further episodes of *torsades de pointes*, and she was discharged with no recurrence of syncope.

1. Monahan BP, Ferguson CL, Killeavy ES, Lloyd BK, Troy J, Cantilena LR. Torsades de pointes occurring in association with terfenadine use. JAMA 1990; 264:2788-2790.

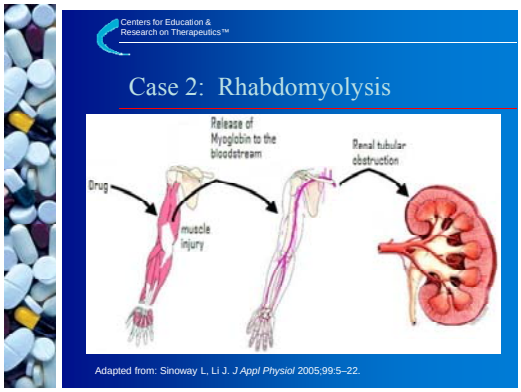


This figure illustrates the time course of the medications that the patient took.[1] Her symptoms started shortly after she began taking ketoconazole. Ketoconazole has not been associated with development of *torsades de pointes* when used as a single agent.

This case was reported to the FDA's MedWatch adverse event reporting system (AERS), and subsequent research and data analysis by FDA scientists resulted in the eventual withdrawal of the drug from the market by the manufacturer.

How did ketoconazole interact with terfenadine to cause QT prolongation and *torsades de pointes* in this patient? That question will be answered during the course of this module.

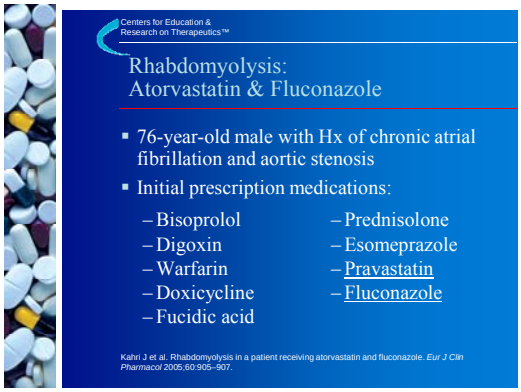
1. Monahan BP, Ferguson CL, Killeavy ES, Lloyd BK, Troy J, Cantilena LR. Torsades de pointes occurring in association with terfenadine use. JAMA 1990; 264:2788-2790.



The second case to be considered is that of potentially lethal skeletal muscle damage, *rhabdomyolysis*, occurring in association with concomitant use of fluconazole (Diflucan®) and atorvastatin (Lipitor®).[1]

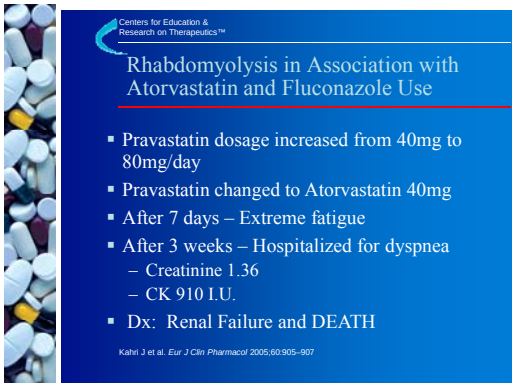
Excessive levels of drugs that inhibit HMG CoA can cause muscle injury by mechanisms that are not entirely clear.[2] This can cause a massive release of myoglobin into the bloodstream, and this protein causes renal tubular obstruction, leading to potentially lethal renal insufficiency or failure.

1. Kahri J, Valkonen M, Backlund T, Vuoristo M, Kivisto KT. Rhabdomyolysis in a patient receiving atorvastatin and fluconazole. Eur J Clin Pharmacol 2005; 60(12):905-907. **2.** Radcliffe KA, Campbell WW. Statin myopathy. Curr Neurol Neurosci Rep 2008; 8(1):66-72.



Two months before admission to the district hospital, the patient was chronically taking nine medicines without any perceived adverse reactions.[1]

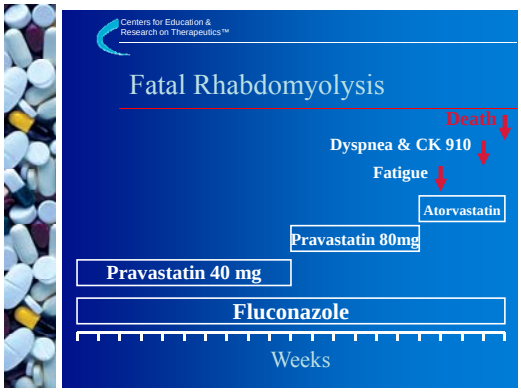
1. Kahri J, Valkonen M, Backlund T, Vuoristo M, Kivisto KT. Rhabdomyolysis in a patient receiving atorvastatin and fluconazole. Eur J Clin Pharmacol 2005; 60(12):905-907.



Because of an inadequate response of the patient's serum low density lipoprotein (LDL) cholesterol (134 mg/dl or 3.47 mmol/l), the patient's dose of pravastatin was doubled from 40 mg/day to 80 mg/day. Six weeks after the change in pravastatin dose, serum LDL cholesterol was 105 mg/dl (2.72 mmol/l) and CK was 58 U/l (reference range, below 270 U/l). In an attempt to achieve a better serum LDL-lowering effect, pravastatin was discontinued and atorvastatin 40 mg/day was prescribed.

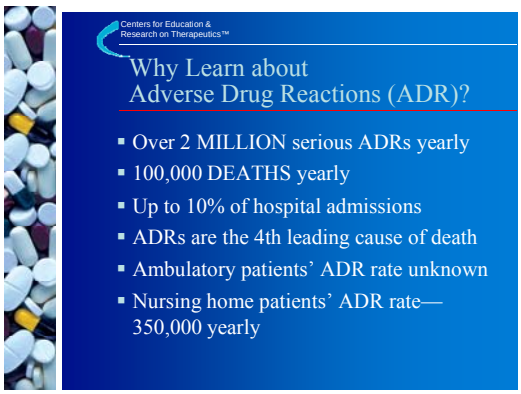
After seven days, the patient developed extreme fatigue and after three weeks the patient complained of severe dyspnea and was hospitalized. The patient's serum creatinine on admission was 1.36 and the creatine kinase was 910 I.U. The patient subsequently developed renal failure and died.[1]

1. Kahri J, Valkonen M, Backlund T, Vuoristo M, Kivisto KT. Rhabdomyolysis in a patient receiving atorvastatin and fluconazole. Eur J Clin Pharmacol 2005; 60(12):905-907.



The graph schematically shows the sequence of drug treatment. After increasing the dose of pravastatin and not reaching the therapeutic target for lower LDL, the treating physician decided to switch the patient to atorvastatin, without changing the chronic regime of fluconazole. Fluconazole, a potent inhibitor of cytochrome P450 3A, resulted in delayed clearance of atorvastatin, an interaction not observed with pravastatin, resulting in rhabdomyolysis, renal failure and death because atorvastatin is more susceptible to CYP3A4 inhibition than pravastatin.[1] Thus, this is an example of a preventable adverse drug interaction had the prescribing physician known about this interaction.

1. Kahri J, Valkonen M, Backlund T, Vuoristo M, Kivisto KT. Rhabdomyolysis in a patient receiving atorvastatin and fluconazole. Eur J Clin Pharmacol 2005; 60(12):905-907.

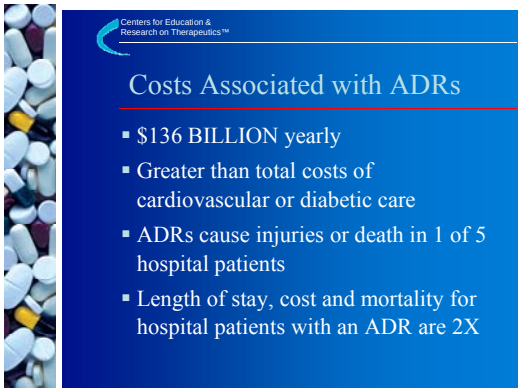


ADRs are one of the leading causes of morbidity and mortality in health care. The Institute of Medicine reported in January of 2000 that from 44,000 to 98,000 deaths occur annually from medical errors.[1] Of this total, an estimated 7,000 deaths occur due to ADRs. To put this in perspective, consider that 6,000 Americans die each year from workplace injuries.

However, other studies conducted on hospitalized patient populations have placed much higher estimates on the overall incidence of serious ADRs. These studies estimate that 6.7% of hospitalized patients have a serious adverse drug reaction with a fatality rate of 0.32%.[2] If these estimates are correct, then there are more than 2,216,000 serious ADRs in hospitalized patients, causing over 106,000 deaths annually. Assuming these statistics are accurate, then ADRs are the fourth leading cause of death in the U.S. – ranked above pulmonary disease, diabetes, AIDS, pneumonia, accidents, and automobile deaths.

Remarkably, these statistics do not include estimates of the number of ADRs that occur in ambulatory settings. Also, it is estimated that over 350,000 ADRs occur in U.S. nursing homes each year.[3, 4] Unfortunately, the U.S. health care system does not provide an accurate estimate of ADRs that occur nationally. However, whatever the true number is, ADRs represent a significant public health problem that is, in many cases, preventable.

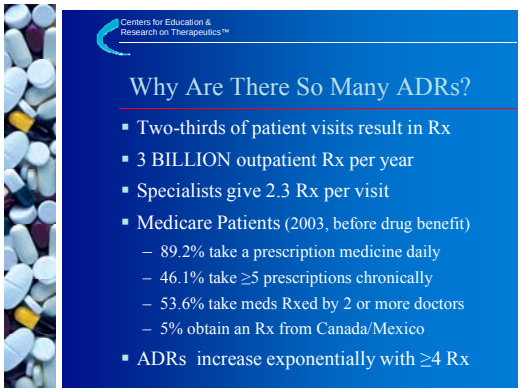
1. Committee on Quality of Health Care in America: Institute of Medicine. To err is human: building a safer health system. National Academy Press 2000. **2**. Lazarou J. Incidence of adverse drug reactions in hospitalized patients: a meta-analysis of prospective studies. JAMA 1998; 279((15):):1200-1205. **3.** Gurwitz JH, Field TS, Avorn J et al. Incidence and preventability of adverse drug events in nursing homes. Am J Med 2000; 109(2):87-94. **4.** Field TS, Gurwitz JH, Avorn J et al. Risk factors for adverse drug events among nursing home residents. Arch Intern Med 2001; 161(13):1629-1634.



In addition to the human costs in morbidity and mortality, the health care costs associated with adverse drug reactions are unacceptably high. Again, methodological constraints limit making highly accurate estimates, but one estimate of the cost of drug-related morbidity and mortality was $177 billion annually in 2000,[1] which is more than the total cost of cardiovascular or diabetic care in the United States. In addition, one out of five injuries or deaths per year to patients WHILE IN THE HOSPITAL may be as a result of ADRs.[2] Finally, a two-fold greater mean length of stay, cost and mortality has been reported for hospitalized patients experiencing an ADR compared to a control group of patients without an adverse drug reaction.[3, 4]

1. Bates DW, Leape LL, Cullen DJ et al. Effect of computerized physician order entry and a team intervention on prevention of serious medication errors [see comments]. JAMA 1998; 280(15):1311-1316. **2.** Brennan TA, Leape LL, Laird NM et al. Incidence of adverse events and negligence in hospitalized patients. Results of the Harvard Medical Practice Study I. New England Journal of Medicine 1991; 324(6):370-376. **3.** Classen DC, Pestotnik SL, Evans RS, Burke JP. Computerized surveillance of adverse drug events in hospital patients. 19911. Qual Saf Health Care 2005; 14(3):221-225. **4.** Classen DC, Pestotnik SL, Evans RS, Lloyd JF, Burke JP. Adverse drug events in hospitalized patients. Excess length of stay, extra costs, and attributable mortality. JAMA 1997; 277(4):301-306.

Preventable Adverse Drug Reactions: A Focus on Drug Interactions



Why are there so many ADRs? Here are just a few of the many reasons.

First, more drugs – and many more combinations of drugs given chronically – are being used to treat patients than ever before. To exemplify this point, 66% of all patient visits to physicians result in prescriptions, and visits to specialists result in 2.3 prescriptions per visit.[1]

Secondly, 3.42 billion prescriptions were filled in the year 2006.[2] That is approximately **11 prescriptions for every person in the United States.**

A survey of 36,901 Medicare patients obtained in 2003 (before Medicare had begun Part D, which provided a prescription drug benefit) gives a snapshot of the extent of prescription drug use by seniors in the U.S. It also demonstrates the complexity of prescribing to this population because of their use of multiple physicians, pharmacies, and sources for their medicines. Overall, 5% of seniors with coverage purchased their medicines from Canada or Mexico, compared to 10.5% of those without a prescription benefit.[3]

Finally, the rate of ADRs increases exponentially after a patient is on four or more medications.[4]

Efforts to reduce unnecessary prescribing are important, but for many patients, the number of medications cannot always be reduced without losing benefit. That is why it is important to understand the basis for drug interactions. This will allow us to make the most appropriate choices in prescribing and avoiding preventable ADRs.

1. Raofi S, Schappert SM. Medication therapy in ambulatory medical care: United States, 2003-04. Vital Health Stat 13 2006;(163):1-40. **2.** NACDS. Prescription Drug Survey. National Association of Chain Drug Stores. 2006. Ref Type: Electronic Citation. **3.** Safran DG, Neuman P, Schoen C, et al. Prescription drug coverage and seniors: findings from a 2003 national survey. Health Aff (Millwood) 2005; Suppl Web Exclusives:W5-166. **4.** Jacubeit T, Drisch D, Weber E. Risk factors as reflected by an intensive drug monitoring system. Agents Actions Suppl 1990; 29:117-25:117-125.

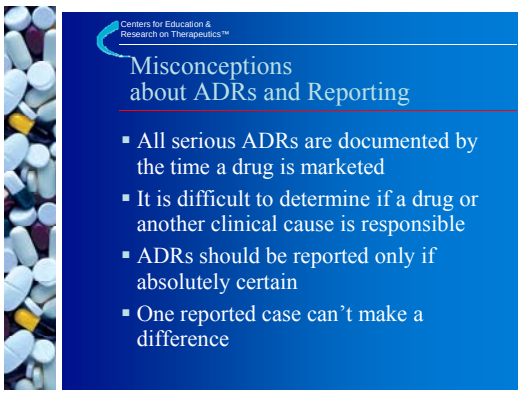
It is worth considering how completely a drug's safety is defined prior to its approval for marketing. When most new drugs are approved, an average of 3000 patients have been exposed to the drug, and many of these are for only relatively short periods of time. However, most drugs that cause serious ADRs do so at very low frequencies, and would require many more exposures to detect the reaction. For example, bromfenac (Duract®) was a non-steroidal anti-inflammatory agent (NSAID) that was removed from the market in 1998, less than one year after it was introduced. Bromfenac caused serious hepatotoxicity in only 1 in 20,000 patients taking the drug for longer than 10 days.[1] As a general rule (the "rule of 3's"), to have some confidence that a drug effect will be observed in the population studied, three times the number of patients need to be exposed. For example, to reliably detect the toxic effects of a drug with a 1 in 20,000 adverse drug reaction frequency, the new drug application database would have to include at least 60,000 patient exposures. That means that **detection of drugs that cause rare toxicity is only practical after, not before, marketing**. For important new drugs, the additional cost and delay of evaluating 60,000 patients is prohibitive.[2]

If one case of hepatotoxicity is seen during pre-marketing testing, it can be difficult, if not impossible, to ascertain whether it was secondary to the drug in question, another co-administered medication, or just the background rate of disease that is seen in the population.

Because the complete safety profile of a new drug will be defined only **after** it has been **approved** and is on the market, it is essential that practitioners watch for and report ADRs throughout the lifecycle of the drug in the market. It is only in this fashion that many serious ADRs are discovered and drug labels are appropriately changed to improve patient safety. Similarly, it is sometimes only through these mechanisms that drugs are removed from the market for serious safety issues. The more and the earlier that this important safety information is received, the earlier that drug safety is enhanced.

1. Clark S. Dangers of non-sedating antihistamines [see comments]. Lancet 1997; 349(9061):1268. **2**. Friedman MA, Woodcock J, Lumpkin MM, et al. The Safety of Newly Approved Medicines: Do Recent Market Removals Mean There Is a Problem? JAMA 1999; 281:1728-1734.

Preventable Adverse Drug Reactions: A Focus on Drug Interactions



Healthcare providers have misconceptions about reporting ADRs.[1-4] These misconceptions include the ideas that:

1) All serious ADRs are documented by the time a drug is marketed;

2) It is hard to determine if a drug is responsible for the ADR;

3) ADRs should be reported only if absolute certainty exists that the ADR is related to a particular drug;

4) One case reported by an individual physician does not contribute to medical knowledge.

Let's look at each one of these points.

1) As we have seen, rare ADRs are usually **NOT** documented by the time a drug is marketed.

2) It can be hard to determine if an individual drug caused a reaction in a complicated patient receiving multiple medications. However, the FDA recommends that, when in doubt about whether a drug caused the reaction, report it.

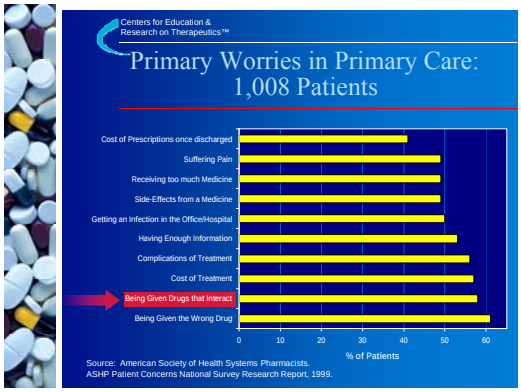
3) A suspicion of an adverse drug reaction should be reported. A healthcare provider does not have to be absolutely certain that a drug caused a reaction. All reports contribute to the heightening of the awareness of FDA safety scientists as they monitor all of the evidence to evaluate the potential for drug-related toxicity. **When in doubt, report!**

4) One individual report **CAN** make a difference. Many drug withdrawals began with one clinical report that initiated further investigation.

1. Figueiras A, Tato F, Fontainas J, Gestal-Otero JJ. Influence of physicians' attitudes on reporting adverse drug events: a case-control study. Med Care 1999; 37(8):809-814. **2.** Eland IA, Belton KJ, van Grootheest AC, Meiners AP, Rawlins MD, Stricker BH. Attitudinal survey of voluntary reporting of adverse drug reactions. Br J Clin Pharmacol 1999; 48(4):623-627. **3.** Eland IA, Sundstrom A, Velo GP et al. Antihypertensive medication and the risk of acute pancreatitis: the European case-control study on drug-induced acute pancreatitis (EDIP). Scand J Gastroenterol 2006; 41(12):1484-1490. **4.** Chyka PA. How many deaths occur annually from adverse drug reactions in the United States? Am J Med 2000; 109(2):122-130.

The inability of the US health care system to adequately limit or prevent serious drug interactions with the concomitant use of drugs has resulted in the removal from the marketplace of dangerous drugs, including terfenadine, mibefradil, astemizole, grepafloxacin, cerivastatin, levomethadyl and cisapride.

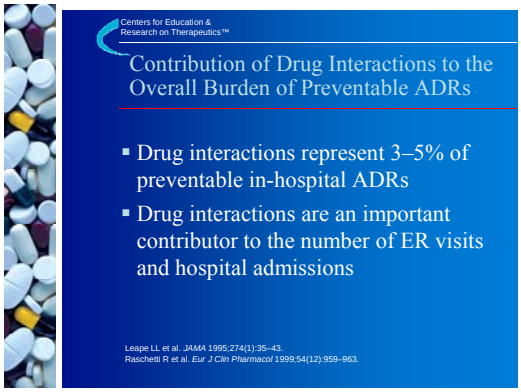
These seven drugs were removed from the market or restricted in their use because it became clear that they continued to be prescribed in an unsafe manner, even after multiple warning letters were disseminated by the manufacturer and the FDA to health care professionals concerning their proper use. Each of these drugs had value in the pharmaceutical marketplace, and each had value to patients. However, because of fatal interactions, the risk associated with continued widespread availability could not be justified.



This figure shows data from a national survey[1] by the American Society of Health Systems Pharmacists (ASHP) that evaluated patient concerns about health systems. This was a random telephone survey of 1,004 adults.

Although the respondents were very concerned about suffering from pain and the cost of filling prescriptions, they were most concerned about being given the wrong drug or that a drug interaction would occur. The public in general has a much greater level of concern about ADRs than most health care providers would suspect.

1. American Society of Health Systems Pharmacists. ASHP Patient Concerns National Survey Research Report. 1999. Bethesda, MD.

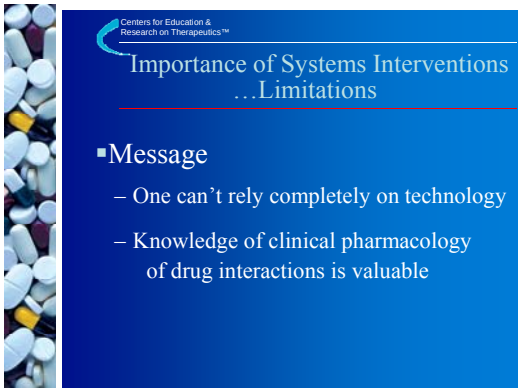


The previous slides have reviewed information about the magnitude of adverse drug reactions and the burden they place on the health care system. How much do drug interactions contribute to the total number of preventable ADRs?

Again, estimates of the numbers of patients injured due to drug interactions vary widely. However, some reasonable estimates come from the work of Dr. Lucien Leape and colleagues.[1] In a systems analysis of ADRs, they estimated that drug-drug interactions represent from 3 to 5% of all in-hospital medication errors. Drug interactions are also an important cause of patient visits to physicians and emergency departments.[2, 3]

1. Leape LL, Bates DW, Cullen DJ et al. Systems analysis of adverse drug events. ADE Prevention Study Group [see comments]. JAMA 1995; 274(1):35-43. **2.** Raschetti R, Morgutti M, Menniti-Ippolito F et al. Suspected adverse drug events requiring emergency department visits or hospital admissions. Eur J Clin Pharmacol 1999; 54(12):959-963. **3.** Budnitz DS, Pollock DA, Weidenbach KN, Mendelsohn AB, Schroeder TJ, Annest JL. National surveillance of emergency department visits for outpatient adverse drug events. JAMA 2006; 296(15):1858-1866.

Preventable Adverse Drug Reactions: A Focus on Drug Interactions

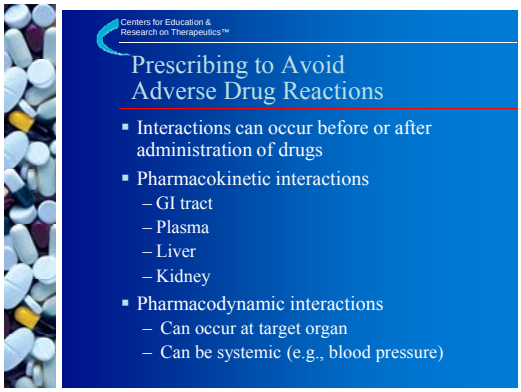


Recent publications have shown that many adverse drug reactions can be prevented and detected through the use of systems interventions. For example, many health systems have instituted new technologies to minimize patient injury due to medication errors and drug-drug interactions.[1-3] Tools like computerized prescription entry[4] and bar coding systems[5] are expected to reduce medical errors and improve outcomes. The potential for reducing medication errors by using computerized medical records as well as drug-interaction screening software that detects and alerts the physician and/or pharmacist to potentially serious drug interactions has been recognized.[6] However, these technological solutions do have limitations. For example, computerized prescription order entry and bar-coding have also been found to facilitate some types of medical errors.[7, 8] The fragmentation of health care delivery may result in incomplete records.

More significant is the fact that even when this information is available, it is not uniformly or optimally incorporated into decision making. This is exemplified in the observation by Cavuto et al. that pharmacists filled prescriptions for interacting drug combinations even though computerized drug interaction software warned not to do so.[9] This has been a persistent problem as shown by Smalley et al., who studied the co-prescription of drugs interacting with cisapride.[10]

These findings reinforce the need for the health care practitioner to develop their own systems approach to preventing undesirable drug interactions. A fundamental understanding of the clinical pharmacology of drug interactions and a framework for avoiding preventable drug interactions remains critically important. Incorporation of up-to-date computerized databases is valuable, and frequent consultation with other members of the health care team, such as nurses and pharmacists, is essential.

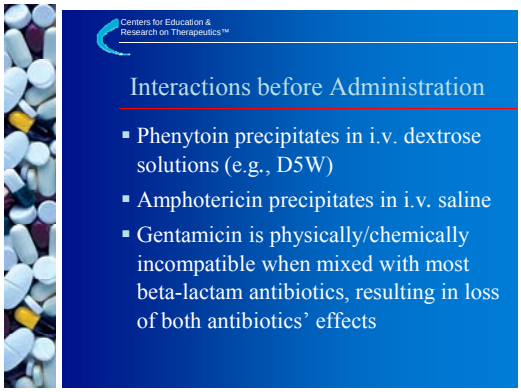
1. Bates DW, Leape LL, Cullen DJ et al. Effect of computerized physician order entry and a team intervention on prevention of serious medication errors [see comments]. JAMA 1998; 280(15):1311-1316. **2.** Evans RS, Pestotnik SL, Classen DC, Horn SD, Bass SB, Burke JP. Preventing adverse drug events in hospitalized patients. Ann Pharmacother 1994; 28(4):523-527. **3.** Patterson ES, Rogers ML, Chapman RJ, Render ML. Compliance with intended use of Bar Code Medication Administration in acute and long-term care: an observational study. Hum Factors 2006; 48(1):15-22. **4.** Bates D.W. Drugs and adverse drug reactions: how worried should we be? JAMA 1998; 279(15):1216-1217. **5.** Patterson ES, Rogers ML, Chapman RJ, Render ML. Compliance with intended use of Bar Code Medication Administration in acute and long-term care: an observational study. Hum Factors 2006; 48(1):15-22. **6.** Committee on Quality of Health Care in America: Institute of Medicine. To err is human: building a safer health system. National Academy Press 2000. **7.** Hey JA, del Prado M, Sherwood J, Kreutner W, Egan RW. Comparative analysis of the cardiotoxicity proclivities of second generation antihistamines in an experimental model predictive of adverse clinical ECG effects [see comments]. Arzneimittelforschung 1996; 46(2):153-158. **8.** Koppel R, Metlay JP, Cohen A et al. Role of computerized physician order entry systems in facilitating medication errors. JAMA 2005; 293(10):1197-1203. **9.** Cavuto NJ, Woosley RL, Sale M. Pharmacies and prevention of potentially fatal drug interactions. JAMA 1996; 275(14):1086-1087. **10.** Taber DF, Jernigan JD, Watson JT, Carr K, Woosley RL. N-desethylacecainide is a metabolite of procainamide in man; convenient method for the preparation of an N-dealkylated drug metabolite. Drug Metab Dispos 1979; 7(5):346.



We will discuss an approach to prescribing drugs in ways that minimize adverse drug interactions as a cause for preventable medication errors.

Drug interactions can occur via several mechanisms:

- Drugs interactions can occur even before drugs enter the body due to drug or formulation incompatibility, or at any point in the process of absorption, distribution, metabolism, and elimination.
- Drugs can bind to each other in IV lines or the GI tract, preventing absorption and reducing systemic availability.
- In theory, drugs could interact in the plasma via protein-bumping reactions, but, despite the emphasis placed in many texts and pharmacology courses, there are very few known clinically relevant examples in which this mechanism is responsible.
- A large number of important interactions do occur in the liver and GI tract due to changes in the rates of drug metabolism brought about by other medicines that are inducers or inhibitors of drug metabolism. We will be looking at this topic in depth.
- Several important interactions occur through competition at drug transporters.
- Finally, interactions can occur at the level of drug action, such as the combination of verapamil, a calcium channel blocker, and a β-blocker. Both slow the heart rate by different mechanisms, and the combination is relatively contraindicated because heart block can result. Because of this interaction, many textbooks and computer programs warn against concomitant use of any β-blocker and any calcium channel blocker. This creates a great deal of confusion and distrust of drug interaction warnings, because most health care providers know that drugs in these two classes are often prescribed successfully and safely in patients with hypertension.



The next few slides will review some of the mechanisms for drug interactions in more detail. Several examples of drug interactions that occur prior to drug administration are listed here.

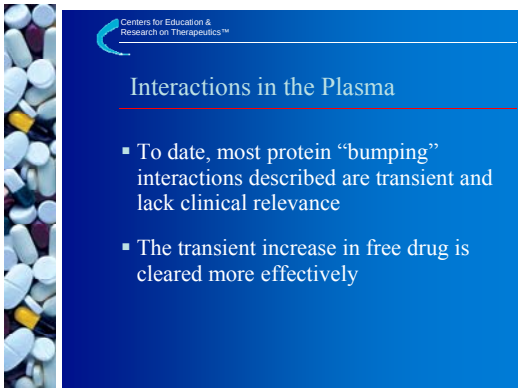
When phenytoin is added to solutions of dextrose, a precipitate of phenytoin forms in the IV bag as an insoluble salt. When this happens, it is no longer able to control seizures.

Amphotericin is still used widely as a urinary bladder perfusion to treat aggressive fungal infections. If it is administered in saline, the drug precipitates and can erode through the bladder wall if not removed. The clinical presentation of such cases is an acute abdomen due to perforation of the bladder (Personal communication, David Flockhart, MD, PhD, University of Indiana, July 2001).

Lastly, aminoglycosides should not be co-mixed in IV fluids with beta-lactam antibiotics because covalent bonds are formed between the two drugs. This can markedly reduce antibiotic efficacy.

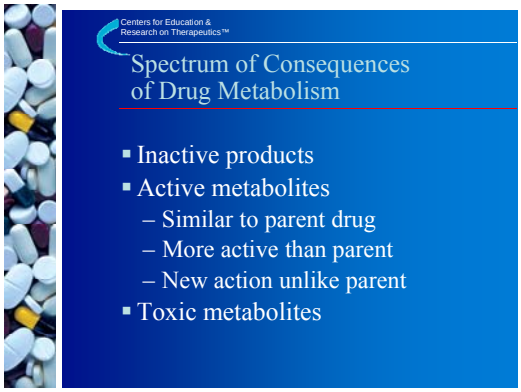
A number of interactions occur in the GI tract and reduce the entry of drugs into the systemic circulation.

Particularly notable among these is the ability of aluminum-containing medicines such as sucralfate (Carafate®) and antacids to reduce the absorption of potentially life-saving antibiotics like ciprofloxacin (Cipro®) and azithromycin (Zithromax®). Women taking iron supplements often do not consider them as a medicine, and should be specifically questioned about whether they are taking iron if they are to be prescribed a quinolone or azithromycin. Drugs such as ketoconazole (Nizoral®) and delavirdine (Rescriptor®) require an acidic environment to be in the non-charged form that is preferentially absorbed. Solubility is drastically reduced in neutral or basic environments that occur when the patient takes medications such as omeprazole (Prilosec®), esomeprazole (Nexium®), lansoprazole (Prevacid®), or H_2-antagonists that raise the stomach's pH.



Some drugs can "bump" other drugs off proteins in the plasma and result in an increased amount of free drug, but for most of the interactions studied, the increase is only transient because the usual elimination mechanisms respond by increasing the rate of elimination.[1] Most of the examples often cited have been subsequently shown to be due to inhibition of elimination, not plasma protein displacement.

1. Hey JA, del Prado M, Sherwood J, Kreutner W, Egan RW. Comparative analysis of the cardiotoxicity proclivities of second generation antihistamines in an experimental model predictive of adverse clinical ECG effects [see comments]. Arzneimittelforschung 1996; 46(2):153-158.



The next few slides will focus on drug metabolism. Some important preventable drug interactions are due to their effects on drug metabolizing enzymes, resulting in either inhibition of the enzyme or induction of the enzyme. There are many potential consequences of changes in drug metabolism for a given drug. It is made more complex by the fact that there are multiple pathways of metabolism for most drugs.

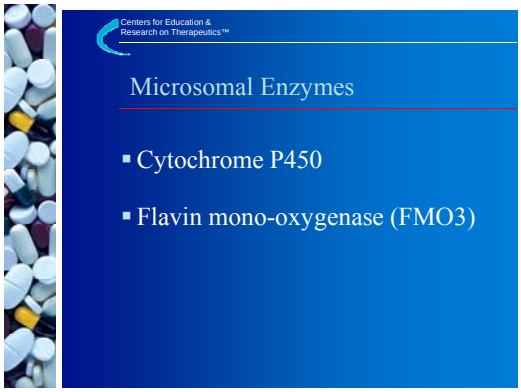
The majority of drugs that are metabolized are converted to inactive metabolites. Of the remaining drugs, some are converted to metabolites that retain the same activity as the parent. An example of this is the active metabolite of terfenadine (Seldane®), fexofenadine (Allegra®) that has equal potency at the histamine receptor and now is on the market and used clinically for allergic rhinitis. However, fexofenadine is more than 50 times less active in blocking potassium channels in the heart and therefore, unlike terfenadine, does not cause *torsades de pointes*.[1]

In some cases, the metabolites are actually more potent than the parent. For example, a pro-drug such as enalapril (Vasotec®) must be hydrolyzed to enalaprilat to become active.

Inhibition of metabolism could result in potentially toxic concentrations of the parent compound. On the other hand, if the parent drug must be metabolized to form the pharmacologically active compound, therapeutic failure could result (as happens, for example, if codeine is not metabolized to morphine[2] or if clopidogrel is not converted to its active metabolite[3]). Induction of drug metabolizing enzymes could similarly result in a sub-therapeutic effect by reducing drug levels below that required for efficacy.

In some cases, the metabolites have entirely new pharmacologic actions not seen with the parent drug. Metabolites can also be toxic, such as the metabolites of acetaminophen which can cause liver injury and failure or the metabolite of meperidine (Demerol®), which can cause seizures.

1. Woosley RL, Chen Y, Freiman JP, Gillis RA. Mechanism of the cardiotoxic actions of terfenadine [see comments]. JAMA 1993 March 24;269(12):1532-6. **2.** Smith RD, Brown BS, Maher RW, Matier WL. Pharmacology of ACC-9653 (phenytoin prodrug). Epilepsia 1989;30:S15-S21. **3.** Savi P, Combalbert J, Gaich C et al. The antiaggregating activity of clopidogrel is due to a metabolic activation by the hepatic cytochrome P450-1A. Thromb Haemost 1994 August;72(2):313-7.



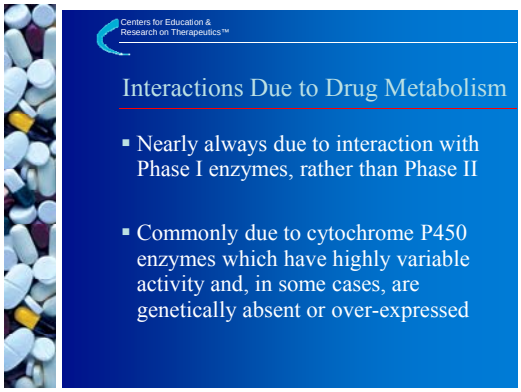
The major group of enzymes in the liver that metabolize drugs can be isolated in a sub-cellular fraction termed the microsomes. The largest and most important of these enzymes are the cytochrome P450 family of enzymes. The origin of the term "cytochrome P450" will be explained later. In addition to cytochrome P450, there are other enzymes in microsomes such as flavin mono-oxygenase (termed FMO3). These are also responsible for metabolism of some drugs, but not as generally important as the cytochrome P450 system.

Drug metabolism is generally classified in two phases, termed Phase I and Phase II.

Phase I reactions include oxidation or reduction reactions, usually through the actions of cytochrome P450 oxidative enzymes or reductases. These enzymes prepare very lipophilic molecules for Phase II enzymatic reactions by creating a site for conjugation, often a reactive group such as a hydroxyl group.

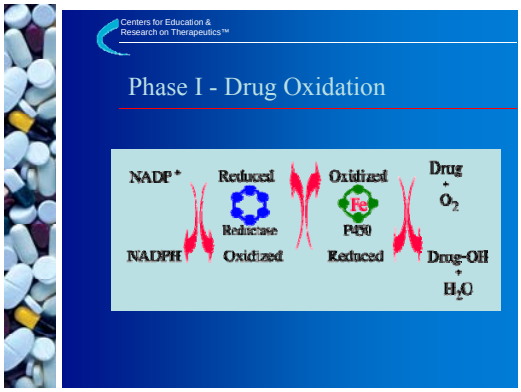
Breakage of bonds in the molecule by reaction with water (hydrolysis), also results in more water-soluble compounds that are often inactive.

Phase II reactions "conjugate" a water-soluble entity such as acetate or glucuronate at the newly created or pre-existing sites on the drug molecule, forming a more polar and water-soluble metabolite that can be more easily excreted in the urine and/or bile.



There are some characteristics of drug metabolism that can help predict important interactions due to inhibition of metabolism. Since Phase II reactions generally result in conjugation of a drug to a water-soluble group like a sugar, peptide (glutathione) or sulfur group, and, because there is a large excess of these groups in well-nourished cells, these reactions are rarely rate-limiting. Thus, they are rarely involved in drug interactions. In contrast, the Phase I reactions carried out by cytochrome P450 enzymes, flavin mono-oxygenases and reductases are more frequently rate limiting. These are the target of clinically significant drug interactions, such as the inhibition of cyclosporine metabolism by erythromycin.

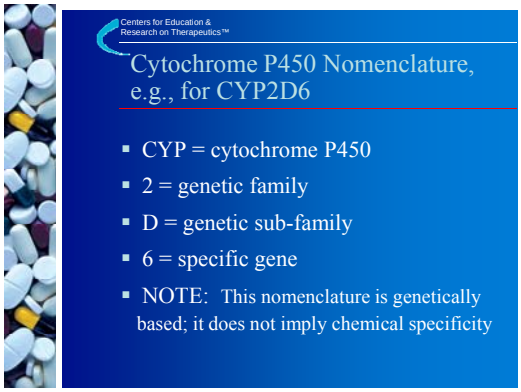
A number of important cytochrome P450 isoforms can be over-expressed or absent in some individuals due to inherited differences. Three of these, CYP2C9, CYP2C19, and CYP2D6, are discussed in the following slides.



There are many different enzymes in the liver microsomes that may be involved in a drug's metabolism. Phase I oxidative enzymes are mostly found in the endoplasmic reticulum, a sub-cellular organelle in the liver. The predominant enzymes responsible for Phase I reactions are those involving the microsomal mixed function oxidation system. This system requires the presence of NADPH and NADPH-cytochrome P450 reductase. "Cytochrome P450" is a super-family of enzymes that is the terminal oxidase of this oxidation system. These enzymes are companions and part of a cascade that shuttles electrons from molecular oxygen in order to oxidize drugs. The word "cytochrome" is derived from the observation that the liver cells appear red because of the iron-containing proteins. The term "P450" comes from the observation that the enzyme absorbs a very characteristic wavelength (450 nm) of UV light when it is exposed to carbon monoxide.

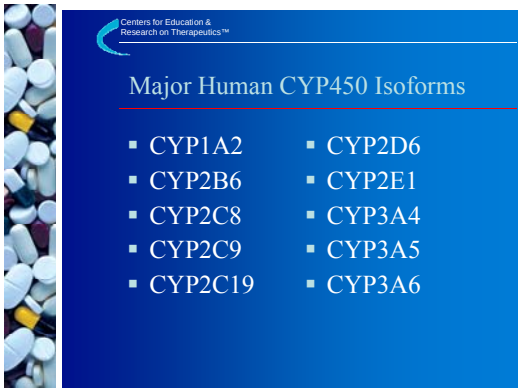
There are many different isoforms of cytochrome P450, but several have been especially well-characterized in terms of clinically relevant drug metabolism and will be discussed here.

As shown in the figure, the enzymes function in a cascade of oxidation-reduction reactions that ultimately result in one atom of oxygen being incorporated into an oxidized metabolite, such as the hydroxylated form of drug shown in the slide as "Drug-OH."

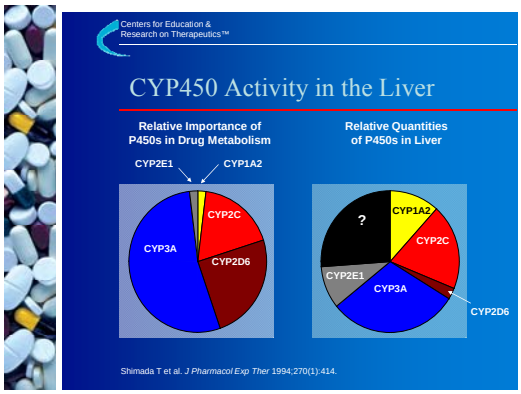


The enzymes in the cytochrome P450 family were named by molecular biologists and protein chemists. The enzymes are named according to the similarity of their amino acid sequences.

A very important principle in pharmacology applies in this case: A small change in the structure of a drug or a protein that interacts with the drug can result in major changes in the actions of the drug. Small changes in amino acid sequence of the enzyme can result in large changes in substrate specificity for the cytochrome P450 enzymes. For example, 2C19 is the principal metabolic enzyme for omeprazole (Prilosec®) metabolism, but a closely related enzyme, 2C9, has no enzymatic activity for inactivating omeprazole. Thus, little functional similarity is imparted by the similarity in amino acid sequence on which this nomenclature is based. However, as will be seen later, there is some concordance between classes of drugs and the P450 family that metabolizes them. The focus of the subsequent slides will be to outline the role of the cytochrome P450 isozymes in metabolism of commonly prescribed drugs, and to identify approaches and tools that can be used in clinical practice to avoid cytochrome P450-mediated drug interactions.



This slide lists the major cytochrome P450 isozymes that are responsible for metabolism of drugs in humans. We will cover a few of these enzymes in some detail. Because many drugs are metabolized principally by these enzymes, important interactions between drugs can be predicted by using a list of drugs that are inhibitors or inducers of that enzyme. This simplifies the search for interacting drugs and provides a framework for prediction of interactions. Such lists can be viewed at www.drug-interactions.com.



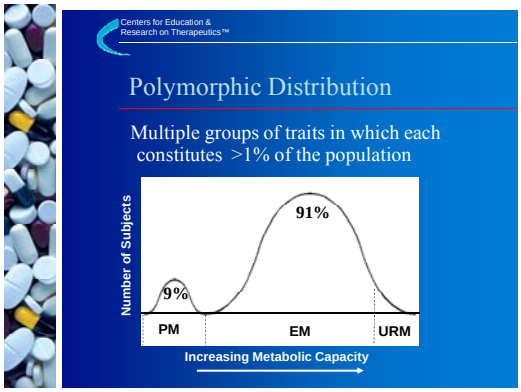
The panel on the left shows some of the major isoforms of CYP450 and the size of the wedge reflects their relative roles in drug metabolism based upon the number of drugs that are known to be metabolized by that particular isozyme. CYP3A is responsible for the metabolism of the largest number of drugs followed by CYP2D6.

The panel on the right summarizes the relative quantity of specific P450 families found in the liver.[1] The CYP3A family is present in the largest amounts. CYP2D6 accounts for less than 2% of the total content of P450 in the liver, but, as shown on the left, is responsible for the metabolism of a large fraction of drugs. A large amount of cytochrome P450 has not yet been characterized.

There is tremendous variability between individuals in terms of expression of cytochrome P450 isozymes. For example, CYP2D6 is not present at all in some human livers and is very highly expressed in others.

Note: 2C on the graph on the right refers to both CYP2C9 and CYP2C19.

1. Shimada T, Yamazaki H, Mimura M, Inui Y, Guengerich FP. Interindividual variations in human liver cytochrome P-450 enzymes involved in the oxidation of drugs, carcinogens and toxic chemicals: studies with liver microsomes of 30 Japanese and 30 Caucasians. J Pharmacol Exp Ther 1994 July;270(1):414-23.



The cytochrome P450 enzymes have three interesting properties that often make it possible to predict drug interactions.

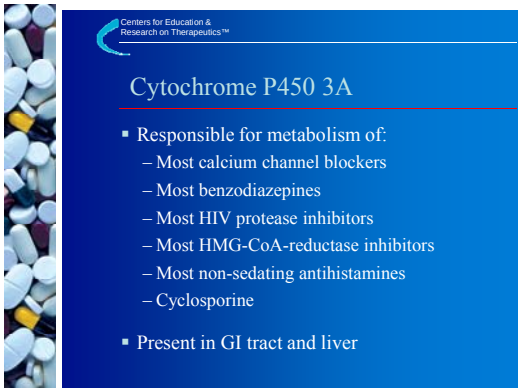
First, some people have mutations or variations in one or more of the nucleic acids in the DNA sequence that expresses a given cytochrome P450 enzyme. As a result, the enzyme may be absent or have low metabolizing activity for drugs that are usually metabolized by that enzyme. If the variant gene is relatively common (more than 1%) it creates a polymorphism -- it literally means that the distribution of the trait has "multiple" "forms" (i.e., "poly"-"morphic"), that each constitute more than 1% of the total population. Any distribution less than 1% is considered a rare or uncommon variant, not a standalone population. At least three of the cytochrome P450s that we will be discussing (2D6, 2C19, 2C9) are polymorphic in their distribution.

This graph demonstrates a population drug metabolism distribution for CYP2D6. On the graph, **PM** means poor metabolizer, **EM** means extensive metabolizer, which is the normal or most common phenotype, and **URM** means ultra-rapid metabolizer. Approximately 7% of the US population has a genetic variant in 2D6 which results in a poor metabolizer phenotype. Ultra-rapid metabolizers usually do not appear as a separate distribution in most phenotypic data. However, they are an important population because when they are administered a usual dose of certain drugs it will be cleared quickly, result in lower blood levels of the drug and, usually, less therapeutic effect. For CYP2D6, it is known that these individuals have very high enzyme activity because they have multiple active copies of the CYP2D6 gene (up to 13 copies have been reported).

Second, people that have usual drug metabolizing ability (EM) can become phenotypic poor metabolizers if they are given a substance (drug or food as we will see later) that inhibits the enzyme. Therefore, if two drugs are administered and they are metabolized by the same enzyme, one can preferentially block access of the other to the enzyme causing the latter to accumulate to higher and potentially toxic levels.

Third, the expression of several of the cytochrome P450 isozymes can be "induced" and result in greatly increased activity. If this occurs, metabolism of any drug that is a substrate for that isozyme will be metabolized more quickly resulting in lower plasma concentrations of the drug. This may also reduce the efficacy of the drug. Also, if the drug is metabolized to a toxic compound, the toxic metabolite may accumulate to higher levels.

The P450 isozymes will now be reviewed in more detail. For printed versions of this module, the accompanying laminated card can be used as a reference for the next few slides. This card can be obtained from www.drug-interactions.com.



CYP3A is responsible for metabolizing the largest number of marketed drugs. These include a wide range of important medications including cyclosporine and HIV protease inhibitors, as well as the no longer marketed non-sedating antihistamines terfenadine (Seldane®) and astemizole (Hismanal®). Although CYP3A does not have polymorphic distribution (it does not have a distinctly separate population as shown in the previous graph), its activity varies over 50-fold in the general population.

CYP3A is the drug-metabolizing pathway involved in the case of *torsades de pointes* and the case of *rhabdomyolysis* described at the beginning of the module.

Terfenadine, the first marketed non-sedating antihistamine, is metabolized by CYP3A to fexofenadine. When the CYP3A-mediated metabolism of terfenadine is inhibited by drugs such as ketoconazole, as in the case described, terfenadine accumulates to high levels. At these high levels, terfenadine is a blocker of potassium channels in the heart.[1] Potassium channels are important for repolarization of heart tissue. When a critical number of these channels are blocked, the QT interval on the electrocardiogram is prolonged and the ventricular arrhythmia *torsades de pointes* can develop, as was seen in this case. Many commonly used drugs can inhibit this enzyme as we will see in the next slide.

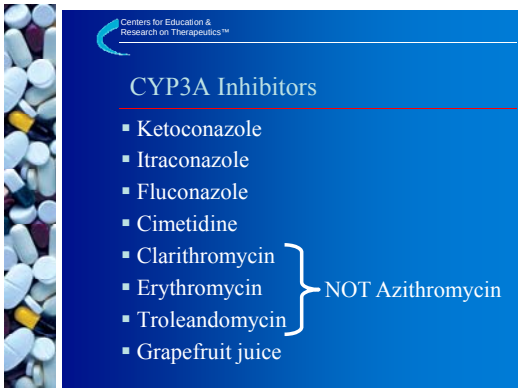
The HMGCoA inhibitor atorvastatin is also metabolized by CYP3A, and in the second case presented earlier, inhibition of this enzyme by fluconazole increased atorvastatin concentration to toxic levels, causing muscle injury.

This important enzyme has been the basis for most of the fatal drug interactions that have gained so much publicity in recent years. For terfenadine, as well as astemizole, mibefradil, levomethadyl and cisapride, recognition and reporting of *torsades de pointes* in association with the drug and their interactions ultimately led to limitations or withdrawal of these drugs from the market.

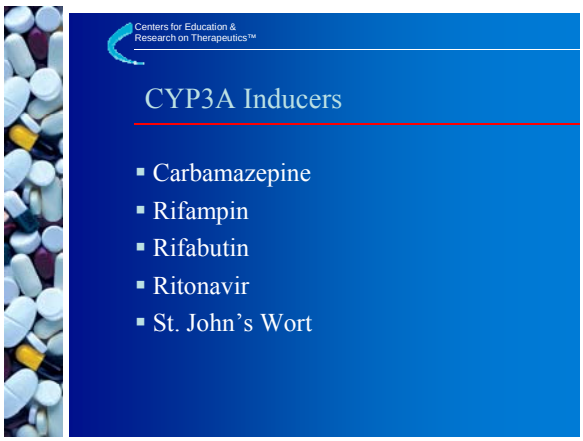
The majority of drugs that may cause cardiac arrhythmias by prolonging the QT interval and the majority of statins are metabolized by cytochrome P450 3A. While the biological basis for this remains unclear, it does make it easier to remember.

Also note that CYP3A is found in the liver and in the GI tract. Drugs that are substrates of CYP3A can be extensively metabolized in the GI tract, and, in fact, the GI tract is responsible for much of the metabolism formerly attributed to the liver. Inhibition of GI tract CYP3A also results in higher plasma levels of substrate drugs.

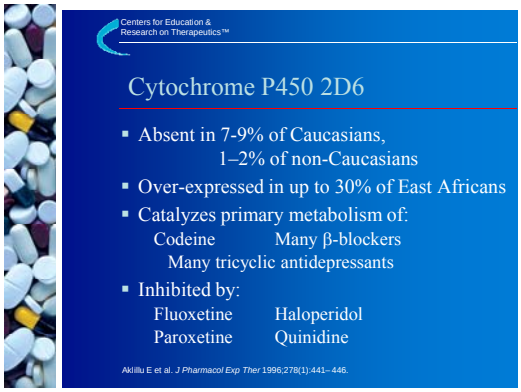
1. Woosley RL, Chen Y, Freiman JP, Gillis RA. Mechanism of the cardiotoxic actions of terfenadine [see comments]. JAMA 1993; 269(12):1532-1536.



These are the important inhibitors of CYP3A that will cause patients to appear phenotypically similar to poor metabolizers. In general, azole antifungal drugs are potent inhibitors of CYP3A, although fluconazole, a potent inhibitor of CYP2C9, is a relatively weak inhibitor of CYP3A, even at high doses. All the macrolide antibiotics, *except azithromycin*, are also potent inhibitors of this cytochrome P450. Cimetidine, unlike ranitidine, is a broad, but relatively weak, inhibitor of many cytochrome P450 enzymes. Also, notice that grapefruit juice is listed as an inhibitor. The role of grapefruit juice in drug interactions will be discussed later.



Several commonly used drugs have been characterized as inducers of CYP3A. Use of these drugs could potentially result in lack of therapeutic efficacy of a CYP3A substrate. Drug interactions with the herbal preparations containing St. John's wort will be discussed later in the presentation.

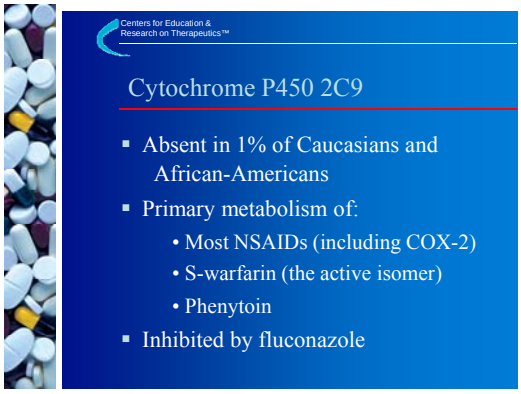


CYP2D6 metabolizes many of the cardiovascular and neurologic drugs in use today. Clinical investigation of CYP2D6 has led to understanding of the reason that codeine fails to relieve pain in some patients. Codeine is actually a pro-drug that is converted to morphine. Codeine itself has only weak analgesic activity and often causes nausea and other adverse effects. The absence of cytochrome P450 2D6 activity in 7 to 9% of many populations means that these individuals cannot metabolize codeine to form the active metabolite morphine. Therefore, they get little, if any, pain relief from codeine.[1] Unfortunately, they will experience codeine's adverse effects, particularly if the dose is increased in the futile attempt to relieve pain.

In a study of Ethiopians, thirty percent were found to have multiple copies (up to 13) of the 2D6 gene and had increased enzyme activity resulting in ultra-rapid metabolism.[2, 3] Ultra-rapid metabolism results in lower blood levels following a standard dose of any drug metabolized by this enzyme. Therefore, these patients may have an inadequate response to standard dosages of β-blockers, narcotic analgesics, or antidepressants and may require higher dosages for clinical effectiveness.

Several commonly used medications inhibit CYP2D6. These include quinidine,[4] fluoxetine, haloperidol and some other antipsychotics.[5, 6] The well-described pharmacokinetic interaction between selective serotonin reuptake inhibitor (SSRI) antidepressants and tricyclic antidepressants appears to be due to the fact that fluoxetine and paroxetine are both potent inhibitors of CYP2D6[7, 8] and render patients phenotypically equivalent to people who do not have the enzyme. This increases the plasma levels of tricyclic antidepressants and increases the potential for side effects. In contrast, patients co-prescribed fluoxetine or paroxetine with codeine may experience no analgesic benefit, since analgesia with codeine requires CYP2D6 for metabolism to morphine.

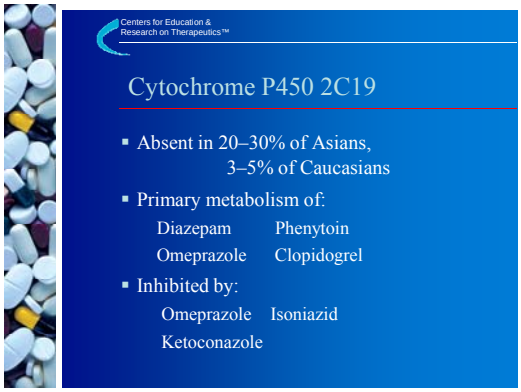
1. Caraco Y, Sheller J, Wood AJ. Pharmacogenetic determination of the effects of codeine and prediction of drug interactions. J Pharmacol Exp Ther 1996; 278(3):1165-1174. **2.** Aklillu E, Persson I, Bertilsson L, Johansson I, Rodrigues F, Ingelman-Sundberg M. Frequent distribution of ultrarapid metabolizers of debrisoquine in an ethiopian population carrying duplicated and multiduplicated functional CYP2D6 alleles. J Pharmacol Exp Ther 1996; 278(1):441-446. **3.** Dalen P, Dahl ML, Bernal Ruiz ML, Nordin J, Bertilsson L. 10-Hydroxylation of nortriptyline in white persons with 0, 1, 2, 3, and 13 functional CYP2D6 genes. Clin Pharmacol Ther 1998; 63(4):444-452. **4.** Branch RA, Adedoyin A, Frye RF, Wilson JW, Romkes M. In vivo modulation of CYP enzymes by quinidine and rifampin. Clin Pharmacol Ther 2000; 68(4):401-411. **5.** Shin JG, Soukhova N, Flockhart DA. Effect of antipsychotic drugs on human liver cytochrome P-450 (CYP) isoforms in vitro: preferential inhibition of CYP2D6. Drug Metab Dispos 1999; 27(9):1078-1084. **6.** Shin JG, Kane K, Flockhart DA. Potent inhibition of CYP2D6 by haloperidol metabolites: stereoselective inhibition by reduced haloperidol. Br J Clin Pharmacol 2001; 51(1):45-52. **7.** Bergstrom RF, Peyton AL, Lemery R. Quantification and mechanism of the fluoxetine and tricyclic antidepressant interaction. CPT 1992; 51:239-248. **8.** Leucht S, Hackl HJ, Steimer W, Angersbach D, Zimmer R. Effect of adjunctive paroxetine on serum levels and side-effects of tricyclic antidepressants in depressive inpatients.. Psychopharmacology (Berl) 2000; 147(4):378-383.



CYP2C9 has a polymorphic distribution, and enzyme activity is missing in 1% of Caucasians and most African-Americans. It is the major enzyme responsible for metabolism of many of the non-steroidal anti-inflammatory drugs (NSAIDs), including the second generation cyclooxygenase-2 (COX-2) specific inhibitors. A number of other important medications have their metabolism primarily catalyzed by CYP2C9. One is warfarin (Coumadin®) and approximately 18% of inter-patient variability in warfarin levels and anticoagulant effects can be explained on the basis of CYP2C9 activity (not the differences in protein binding as originally thought). Most of the traditional NSAIDs, such as ibuprofen, and the COX-2 specific drugs are metabolized by CYP2C9.

The azole antifungal agent fluconazole (Diflucan®) is a potent inhibitor of CYP2C9 and can result in serious drug interactions, as demonstrated in the second case presented earlier. Conventional doses of fluconazole abolish CYP2C9 activity. An interaction between fluconazole and warfarin results in at least a two-fold increase in warfarin blood level, a reduction in warfarin clearance, and increased anticoagulation.[1] Clinical studies have identified a significant interaction between fluconazole and celecoxib (Celebrex®), leading to a two-fold increase in celecoxib plasma concentrations.[2] A clinical pharmacokinetic study showed an increase in phenytoin area under the plasma concentration curve (AUC) following fluconazole administration,[3] and phenytoin toxicity has been reported with concomitant administration of fluconazole and phenytoin.[4]

1. Black DJ, Kunze KL, Wienkers LC et al. Warfarin-Fluconazole II (A Metabolically Based Drug Interaction: In Vivo Studies). Drug Metabolism and Disposition 1996; 24(4):422-428. **2.** Davies NM, McLachlan AJ, Day RO, Williams KM. Clinical pharmacokinetics and pharmacodynamics of celecoxib: a selective cyclo-oxygenase-2 inhibitor. Clin Pharmacokinet 2000; 38(3):225-242. **3.** Touchette MA, Chandrasekar PH, Milad MA, Edwards DJ. Contrasting effects of fluconazole and ketoconazole on phenytoin and testosterone disposition in man. Br J Clin Pharmacol 1992; 34(1):75-78. **4.** Cadle RM, Zenon GJ, III, Rodriguez-Barradas MC, Hamill RJ. Fluconazole-induced symptomatic phenytoin toxicity. Ann Pharmacother 1994; 28(2):191-195.

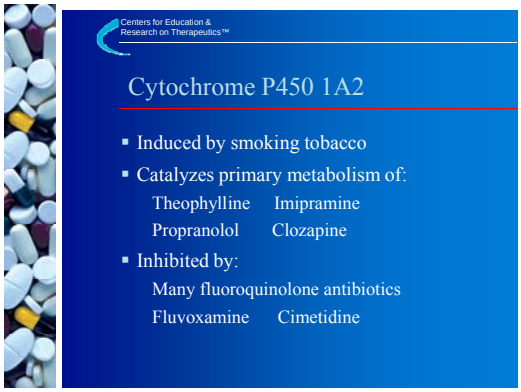


The cytochrome P450 2C19 enzyme is notable because of its genetically-determined absence in such a high percentage of Asians (approximately 20-30%). This enzyme metabolizes many anticonvulsants, diazepam (Valium®), omeprazole (Prilosec®) and several of the tricyclic antidepressants. Asians have reduced clearance of diazepam compared to Caucasians,[1] and a survey of Asian and Western physicians found the use of lower doses of diazepam in Asians.[2] Asian patients may have a lower omperazole dosage requirement for effective treatment of *Helicobacter Pylori*. Asians can have about a four-fold higher plasma concentrations of omeprazole compared to Caucasians and one should consider dosage adjustment if response is sub-optimal.[3] In addition, the poor metabolizer genotype for CYP2C19 resulted in a higher cure rate for H. Pylori than in those with the rapid metabolizer genotype in an Asian population treated with omeprazole as part of dual therapy.[4] Similar results have been shown with proton pump inhibitors in a triple therapy regimen.[5]

Ketoconazole[6] and omeprazole[7] are inhibitors of CYP2C19, and have the potential for clinically significant interactions with substrates of CYP2C19 such as diazepam[8] or phenytoin.[9] Isoniazid, used to treat tuberculosis, is an inhibitor of CYP2C19[10] and should be prescribed cautiously to patients taking phenytoin and other drugs metabolized by CYP2C19.[11]

1. Ghoneim MM, Korttila K, Chiang CK et al. Diazepam effects and kinetics in Caucasians and Orientals. Clin Pharmacol Ther 1981; 29(6):749-756. **2.** Rosenblat R, Tang SW. Do Oriental psychiatric patients receive different dosages of psychotropic medication when compared with occidentals. Can J Psychiatry 1987; 32(4):270-274. **3.** Wang JH, Li PQ, Fu QY, Li QX, Cai WW. Cyp2c19 genotype and omeprazole hydroxylation phenotype in Chinese Li population. Clin Exp Pharmacol Physiol 2007; 34(5-6):421-424. **4.** Furuta T., Ohashi K, Kamata T. et al. Effect of genetic differences in omeprozole metabolism on cure rates for *helicobacter pylori* infection and peptic ulcer. Annals of Internal Med 1998; 129(12):1027-1030. **5.** Furuta T., Shirai N, Takashima M et al. Pharmacogenetics amd Genomics: Effect of genotypic differences in CYP2C19 on cure rates for Helicobacter pylori infection by triple therapy with a proton pump inhibitor, amoxicillin, and clarithromycin. Clinical Pharacology & Therapeutics 2001; 69:158-168. **6.** Atiba JO, Blaschke TF, Wilkinson GR. Effects of ketoconazole on the polymorphic 4-hydroxylations of S-mephenytoin and debrisoquine. Br J Clin Pharmacol 1989; 28(2):161-165. **7.** Ko JW, Sukhova N, Thacker DL, Chen P, Flockhart DA. Evaluation of Omeprazole and Lansoprazole as inhibitors of Cytochrome P450 isoforms. Drug Metab Dispos 1997; 25(7):853-862. **8.** Ishizaki T, Chiba K, Manabe K et al. Comparison of the interaction potential of a new proton pump inhibitor, E3810, versus omeprazole with diazepam in extensive and poor metabolizers of S-mephenytoin 4'-hydroxylation. Clin Pharmacol Ther 1995; 58(2):155-164. **9.** Prichard PJ, Walt RP, Kitchingman GK et al. Oral phenytoin pharmacokinetics during omeprazole therapy. Br J Clin Pharmacol 1987; 24(4):543-545. **10.** Desta Z, Soukhova NV, Flockhart DA. Inhibition of cytochrome P450 (CYP450) isoforms by isoniazid: potent inhibition of CYP2C19 and CYP3A. Antimicrob Agents Chemother 2001; 45(2):382-392. **11.** Payne, C. D., et al. "Increased active metabolite formation explains the greater platelet inhibition with prasugrel compared to high-dose clopidogrel." J.Cardiovasc.Pharmacol. 50.5 (2007): 555-62.

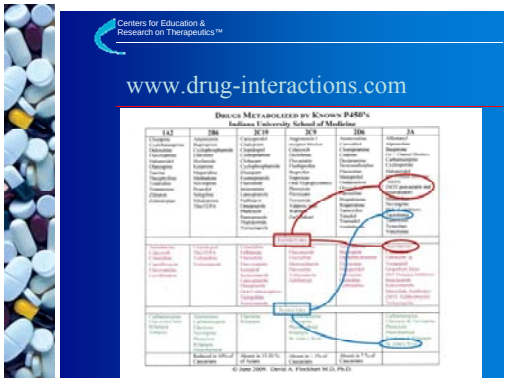
Preventable Adverse Drug Reactions: A Focus on Drug Interactions



Cytochrome P450 1A2 is an important hepatic drug-metabolizing enzyme that metabolizes many commonly used drugs including theophylline, imipramine, propranolol, and clozapine. CYP1A2 is induced in a clinically significant manner by tobacco smoking. The clearance of theophylline, imipramine, propranolol and clozapine are all increased by smoking. Thus, people who smoke tobacco may require higher doses of some medications that are substrates of CYP1A2. In contrast, a smoker would require a decrease in theophylline dosage if, for example, smoking were discontinued and the enzyme is no longer induced. This topic has been reviewed by Benowitz et al., and Tricker.[1, 2]

Inhibitors of CYP1A2, including some fluoroquinolone antibiotics, can increase the plasma concentrations of drugs that are metabolized by CYP1A2, with a potential for increased toxicity.[3, 4]

1. Benowitz NL, Peng M, Jacob P, III. Effects of cigarette smoking and carbon monoxide on chlorzoxazone and caffeine metabolism. Clin Pharmacol Ther 2003; 74(5):468-474. **2.** Tricker AR. Nicotine metabolism, human drug metabolism polymorphisms, and smoking behaviour. Toxicology 2003; 183(1-3):151-173. **3.** Raaska K, Neuvonen PJ. Ciprofloxacin increases serum clozapine and N-desmethylclozapine: a study in patients with schizophrenia. Eur J Clin Pharmacol 2000; 56(8):585-589. **4.** Grasela TH, Jr., Dreis MW. An evaluation of the quinolone-theophylline interaction using the Food and Drug Administration spontaneous reporting system. Arch Intern Med 1992; 152(3):617-621.



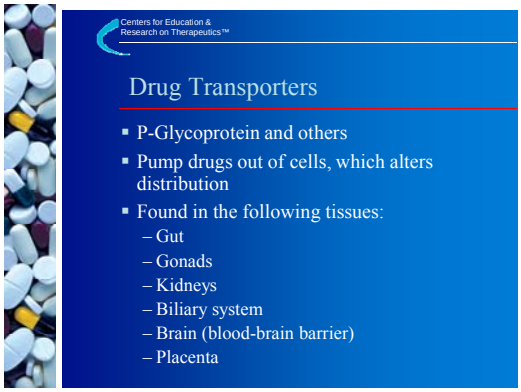
It would be impossible to memorize all drug interactions, even the small number presented here. Fortunately, there are aids to help health care providers to prevent drug interactions, such as the one shown here. The slide shows a pocket version of a much larger CYP P450 drug interaction table available at www.drug-interactions.com. This table includes a listing of the six major cytochrome P450 isozymes involved in drug metabolism and many of the drugs that are metabolized by them. We recommend using this or another table as a quick reference for an initial screen for potential drug interactions.

If two drugs are metabolized by the same cytochrome P450, it is very possible that competitive inhibition could lead to higher-than-usual levels of either or both of the drugs. If a drug is metabolized by a specific cytochrome P450 and is taken with an inhibitor or inducer of that enzyme, an interaction is also likely.

The following are examples of how to use this card. If a patient is taking amiodarone and requires a statin agent to decrease cholesterol (follow the red indicators above), the card shows that amiodarone is an inhibitor of CYP2D6 and CYP3A. Also note that lovastatin, atorvastatin, and simvastatin are metabolized by CYP3A, and that if it is administered with amiodarone (an inhibitor of CYP3A) a toxic level of the statin may occur. The result may be an adverse reaction (rhabdomyolysis or liver toxicity). The best choice among statins in this case would be pravastatin because it is not metabolized by CYP3A.

Another example can be seen if a transplant patient were taking tacrolimus and asks to take St. John's wort (follow blue indicators above). As seen on the card, St. John's wort induces CYP3A4. The concomitant administration of St John's wort with some protease inhibitors can result in the induction of CYP3A4, increased metabolism, and sub-therapeutic levels of the protease inhibitor.

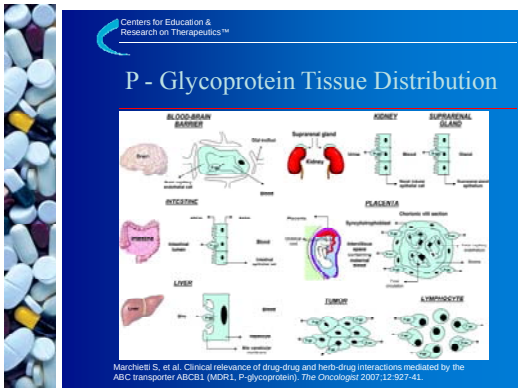
Preventable Adverse Drug Reactions: A Focus on Drug Interactions



P Glycoprotein (PGP) was first identified by Juliano and Ling in 1976 as a surface glycoprotein in Chinese hamster ovary cells expressing the cancer Multi-Drug Resistance (MDR) phenotype.[1] Cloning of the encoding gene and structure analysis of the protein revealed that PGP is a 160-kDa ATP-dependent efflux transporter, belonging to the ABC (ATP Binding Cassette) superfamily.[2]

PGP plays an important role in the distribution and excretion of many endogenous compounds and drugs, especially in the gut. It also is responsible for preventing drugs from entering the brain, i.e., the blood-brain barrier.[3-5] Prescription and OTC drugs, foods and endogenous compounds may be substrates, inhibitors and/or inducers of these transporters.[6]

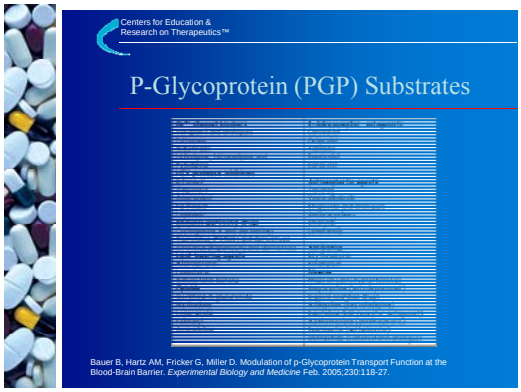
1. Juliano RL, Ling V. A surface glycoprotein modulating drug permeability in Chinese hamster ovary cell mutants. **2.** Biochim Biophys Acta 1976; 455(1):152-162. **3.** Juranka PF, Zastawny RL, Ling V. P-glycoprotein: multidrug-resistance and a superfamily of membrane-associated transport proteins. FASEB J 1989; 3(14):2583-2592. **4.** Marchetti S, Mazzanti R, Beijnen JH, Schellens JH. Concise review: Clinical relevance of drug drug and herb drug interactions mediated by the ABC transporter ABCB1 (MDR1, P-glycoprotein). Oncologist 2007; 12(8):927-941. **5.** Ronaldson PT, Persidsky Y, Bendayan R. Regulation of ABC membrane transporters in glial cells: Relevance to the pharmacotherapy of brain HIV-1 infection. Glia 2008. **6.** Roberts LM, Black DS, Raman C et al. Subcellular localization of transporters along the rat blood-brain barrier and blood-cerebral-spinal fluid barrier by in vivo biotinylation. Neuroscience 2008.



The anatomical localization of PGP suggests that it can play a physiological role in detoxification and protection against toxic xenobiotics and metabolites. It is found in various tumors where it confers the multi-drug resistance (MDR) phenotype. It is also found in the apical/luminal membrane of polarized cells in several normal human tissues with excretory function (liver, kidney, adrenal gland) and barrier function (intestine, blood-brain barrier, placenta, blood–testis and blood–ovarian barriers). Excreting foreign compounds into bile, urine, and the intestinal lumen prevents their accumulation in the brain, testis, and fetus and can protect the organism against harm.[1]

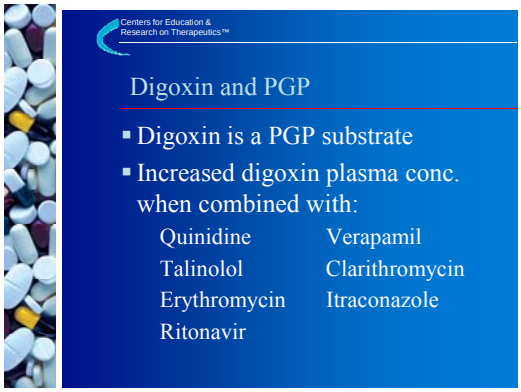
1. Marchetti S, Mazzanti R, Beijnen JH, Schellens JH. Concise review: Clinical relevance of drug drug and herb drug interactions mediated by the ABC transporter ABCB1 (MDR1, P-glycoprotein). Oncologist 2007; 12(8):927-941.

Preventable Adverse Drug Reactions: A Focus on Drug Interactions



When researchers started compiling a list of PGP substrates, it became clear that a substantial proportion of known PGP substrates are also subject to metabolic transformation by CYP3A isozymes.[1, 2] The overlap in substrate specificity between PGP and CYP3A also extends to similar expression patterns in tissues. Co-expression of the two in hepatocytes and in the gut wall is of particular importance. This combination of active efflux via PGP and metabolic biotransformation by CYP3A reduces the oral bioavailability of numerous pharmacologic agents. Additionally, the potential for augmentation of unwanted drug-drug interactions is possible with this co-expression in barrier tissues.[3]

1. Kim RB, Wandel C, Leake B et al. Interrelationship between substrates and inhibitors of human CYP3A and P-glycoprotein. Pharm Res 1999; 16(3):408-414. **2.** Bauer B, Hartz AM, Fricker G, Miller DS. Modulation of p-glycoprotein transport function at the blood-brain barrier. Exp Biol Med (Maywood) 2005; 230(2):118-127. **3.** Callaghan R, Crowley E, Potter S, Kerr ID. P-glycoprotein: so many ways to turn it on. J Clin Pharmacol 2008; 48(3):365-378.



The combination of digoxin and quinidine (or digoxin with verapamil, clarithromycin, erythromycin, itraconazole) has been shown to produce increased plasma concentrations and lower renal clearance of digoxin.[1-4]

Talinolol has been shown to reduce renal clearance and the area under the concentration-time curve (AUC) of digoxin in plasma.[5]

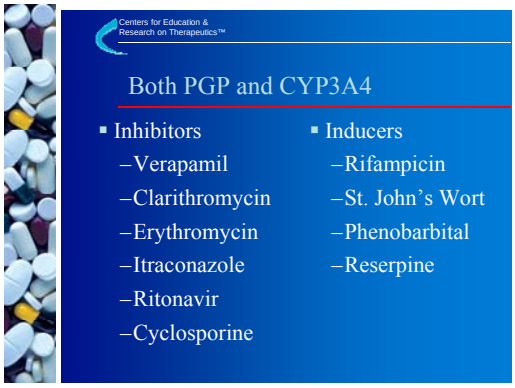
Ritonavir also reduces clearance, increases the plasma AUC of digoxin and predisposes to digoxin toxicity.[6, 7]

In addition to digoxin, many other drugs are affected by PGP transport inhibitors. Since Verapamil is both a PGP and a CYP3A inhibitor, it increases the risk of tacrolimus toxicity.[8, 9]

Quinidine also increases central nervous system adverse effects produced by loperamide (Immodium®), an opioid drug that is usually not capable of passing the blood-brain barrier.[10, 11]

Interestingly, proton pump inhibitors (PPIs) like pantoprazole (Protonix®) and omeprazole (Prilosec®) inhibit PGP and another transporter termed breast cancer resistance protein (BCRP). PPIs have been shown to increase methotrexate's AUC.[12]

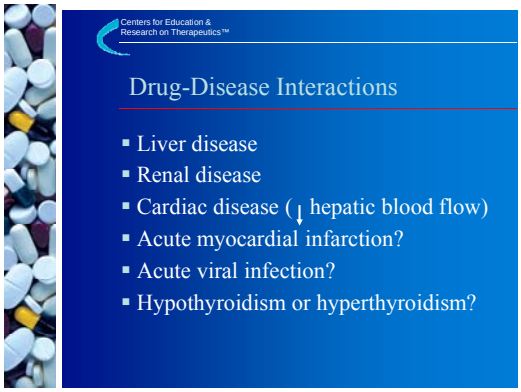
1. Marchetti S, Mazzanti R, Beijnen JH, Schellens JH. Concise review: Clinical relevance of drug drug and herb drug interactions mediated by the ABC transporter ABCB1 (MDR1, P-glycoprotein). Oncologist 2007; 12(8):927-941. **2.** Callaghan R, Crowley E, Potter S, Kerr ID. P-glycoprotein: so many ways to turn it on. J Clin Pharmacol 2008; 48(3):365-378. **3.** Leahey EBJr, Reiffel JA, Giardina E-GV, Bigger JT, Jr. The effect of quinidine and other oral antiarrhythmic drugs on serum digoxin. A prospective study. Ann Intern Med 1980; 92:605-608. **4.** Doering W. Quinidine-digoxin interaction: Pharmacokinetics, underlying mechanism and clinical implications. N Engl J Med 1979; 301(8):400-404. **5.** Westphal K, Weinbrenner A, Giessmann T et al. Oral bioavailability of digoxin is enhanced by talinolol: evidence for involvement of intestinal P-glycoprotein. Clin Pharmacol Ther 2000; 68(1):6-12. **6.** Phillips EJ, Rachlis AR, iTO s. Digoxin toxicity and ritonavir: a drug interaction mediated through p-glycoprotein? AIDS 2003; 17(10):1577-1578. **7.** Ding R, Tayrouz Y, Riedel KD et al. Substantial pharmacokinetic interaction between digoxin and ritonavir in healthy volunteers. Clin Pharmacol Ther 2004; 76(1):73-84. **8.** Kempf DJ, Marsh KC, Kumar G et al. Pharmacokinetic enhancement of inhibitors of the human immunodeficiency virus protease by coadministration with ritonavir. Antimicrob Agents Chemother 1997; 41(3):654-660. **9.** Moise NS, Moon PF, Flahive WJ et al. Phenylephrine-induced ventricular arrhythmias in dogs with inherited sudden death. J Cardiovasc Electrophysiol 1996; 7(3):217-230. **10.** Hellstrom L, Blaak E, Hagstrom-Toft E. Gender differences in adrenergic regulation of lipid mobilization during exercise. Int J Sports Med 1996; 17(6):439-447. **11.** Leahey EBJr, Reiffel JA, Giardina E-GV, Bigger JT, Jr. The effect of quinidine and other oral antiarrhythmic drugs on serum digoxin. A prospective study. Ann Intern Med 1980; 92:605-608. **12**. Joerger M, Huitema AD, van den Bongard HJ et al. Determinants of the elimination of methotrexate and 7-hydroxy-methotrexate following high-dose infusional therapy to cancer patients. Br J Clin Pharmacol 2006 July;62(1):71-80



In addition to serving as substrates, there are compounds capable of inducing or inhibiting the expression of both PGP and CYP3A.[1, 2] Rifampicin has been shown to reduce both plasma concentrations and AUC of digoxin, talinolol and tacrolimus.[3-5]

St. John's wort is capable of increasing plasma concentrations of digoxin, cyclosporine, indinavir and tacrolimus.[6-11]

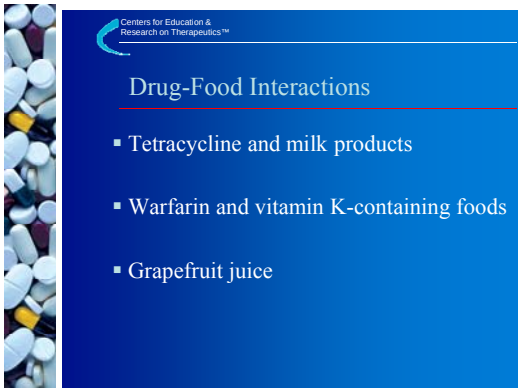
1. Marchetti S, Mazzanti R, Beijnen JH, Schellens JH. Concise review: Clinical relevance of drug drug and herb drug interactions mediated by the ABC transporter ABCB1 (MDR1, P-glycoprotein). Oncologist 2007; 12(8):927-941. **2.** Callaghan R, Crowley E, Potter S, Kerr ID. P-glycoprotein: so many ways to turn it on. J Clin Pharmacol 2008; 48(3):365-378. **3.** Westphal K, Weinbrenner A, Giessmann T et al. Oral bioavailability of digoxin is enhanced by talinolol: evidence for involvement of intestinal P-glycoprotein. Clin Pharmacol Ther 2000; 68(1):6-12. **4.** Greiner B, Eichelbaum M, Fritz P et al. The role of intestinal P-glycoprotein in the interaction of digoxin and rifampin. J Clin Invest 1999; 104(2):147-153. **5.** Hebert MF, Fisher RM, Marsh CL, Dressler D, Bekersky I. Effects of rifampin on tacrolimus pharmacokinetics in healthy volunteers. J Clin Pharmacol 1999; 39(1):91-96. **6.** Johne A, Brockmoller J, Bauer S, Maurer A, angheinrich M, Roots I. Pharmacokinetic interaction of digoxin with an herbal extract from St John's wort (Hypericum perforatum). Clin Pharmacol Ther 1999; 66(4):338-345. **7.** Durr D, Stieger B, Kullak-Ublick GA et al. St John's Wort induces intestinal P-glycoprotein/MDR1 and intestinal and hepatic CYP3A4. Clin Pharmacol Ther 2000; 68(6):598-604. **8.** Ruschitzka F, Meier PJ, Turina M, Luscher TF, Noll G. Acute heart transplant rejection due to Saint John's wort. Lancet 2000; 355(9203):548-549. **9.** Carlson AM, Morris LS. Coprescription of terfenadine and erythromycin or ketaconazole: an assessment of potential harm. J Am Pharm Assoc (Wash) 1996; NS36(4):263-269. **10.** Bauer S, Stormer E, Johne A et al. Alterations in cyclosporin A pharmacokinetics and metabolism during treatment with St John's wort in renal transplant patients. Br J Clin Pharmacol 2003; 55(2):203-211. **11.** Moss AJ, Hall WJ, Cannom DS et al. Improved survival with an implanted defibrillator in patients with coronary disease at high risk for ventricular arrhythmia. Multicenter Automatic Defibrillator Implantation Trial Investigators [see comments]. N Engl J Med 1996; 335(26):1933-1940.



In addition to the drug-drug interactions just reviewed, drug-disease interactions can occur. These include interactions between certain drugs and specific disease states. Severe liver disease can be associated with reduced metabolic clearance and higher plasma levels of drugs extensively metabolized by the liver.[1] The effects of renal disease on elimination of drugs that are primarily cleared renally are more predictable, and well-established guidelines exist for dosage adjustment of many drugs in renal disease.[2] Heart failure reduces liver blood flow and causes a reduction in clearance for drugs such as lidocaine or propranolol that are usually extensively cleared by the liver,[3, 4] and acute myocardial infarction reduces clearance of some drugs, such as lidocaine.[5] Acute viral infection and changes in thyroid function have been associated with altered clearance for some drugs, such as theophylline and warfarin.[6-8] However, the results are so variable between individuals that it is hard to predict who is at risk, and these changes are usually only clinical important in cases of extremely impaired organ function.

1. Frye RF, Zgheib NK, Matzke GR et al. Liver disease selectively modulates cytochrome P450-mediated metabolism. Clin Pharmacol Ther 2006; 80(3):235-245. **2.** Brater DC. Drug dosing in patients with impaired renal function. Clin Pharmacol Ther 2009; 86(5):483-9. **3.** Cascorbi I, Paul M, Kroemer HK. Pharmacogenomics of heart failure -- focus on drug disposition and action. Cardiovasc Res 2004; 64(1):32-39. **4.** Iervasi G, Clerico A, Bonini R et al. Acute effects of amiodarone administration on thyroid function in patients with cardiac arrhythmia. J Clin Endocrinol Metab 1997; 82(1):275-280. **5.** Bates DW, Spell N, Cullen DJ et al. The costs of adverse drug events in hospitalized patients. Adverse Drug Events Prevention Study Group [see comments]. JAMA 1997; 277(4):307-311. **6.** Kim RB, Fromm MF, Wandel C et al. The drug transporter P-glycoprotein limits oral absorption and brain entry of HIV-1 protease inhibitors. J Clin Invest 1998; 101(2):289-294. **7.** Stephens MA, Self TH, Lancaster D, Nash T. Hypothyroidism: effect on warfarin anticoagulation. South Med J 1989; 82(12):1585-1586. **8.** Yamaguchi A, Tateishi T, Okano Y et al. Higher incidence of elevated body temperature or increased C-reactive protein level in asthmatic children showing transient reduction of theophylline metabolism. J Clin Pharmacol 2000; 40(3):284-289.

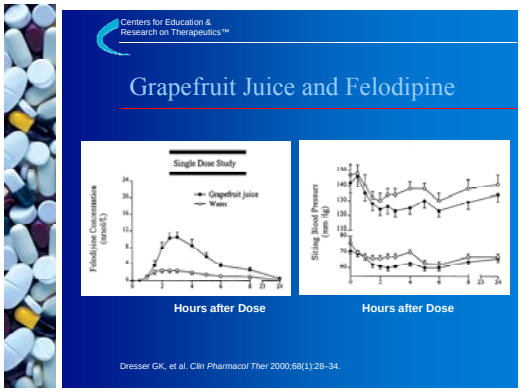
Preventable Adverse Drug Reactions: A Focus on Drug Interactions



Several drugs are known to interact with foods,[1] some of which are listed here. One of the early observations was the reduced absorption of tetracycline when taken with milk products. The chelation of tetracycline by calcium in milk and other dairy products prevents it from being absorbed from the intestines. Dietary sources of vitamin K, such as spinach or broccoli, may increase the dosage requirement for warfarin by a pharmacodynamic antagonism of its effect. Patients should be counseled to maintain a consistent diet during warfarin therapy and refrain from eating green leafy vegetables.

Grapefruit juice contains bergamottin, a bioflavonoid that inhibits CYP3A and blocks the metabolism of many drugs. This was first described for felodipine (Plendil®)[2] but has now been observed with several drugs.[3] This interaction can lead to reduced clearance and higher blood levels when the drugs are taken simultaneously with grapefruit juice. With regular consumption, grapefruit juice also reduces the expression of CYP3A in the GI tract and contributes to the interaction.[4]

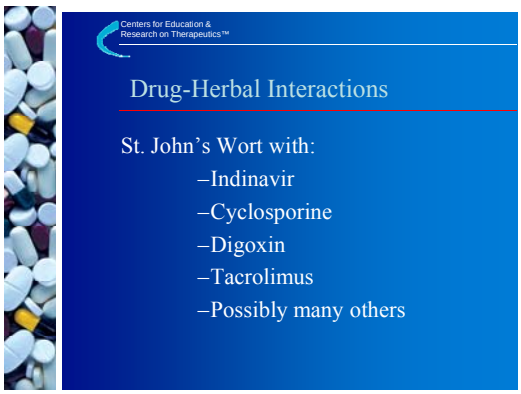
1. Locati EH, Zareba W, Moss AJ et al. Age- and sex-related differences in clinical manifestations in patients with congenital long-QT syndrome: findings from the International LQTS Registry. Circulation 1998; 97(22):2237-2244. **2.** Bailey DG, Malcolm J, Arnold O, Spence JD. Grapefruit juice-drug interactions. 1998. Br J Clin Pharmacol 2004; 58(7):S831-S840. **3.** Bailey DG, Spence JD, Munoz C, Arnold JM. Interaction of citrus juices with felodipine and nifedipine. Lancet 1991; 337(8736):268-269. **4.** Lown KS, Bailey DG, Fontana RJ et al. Grapefruit Juice Increases Felodipine Oral Availability in Humans by Decreasing Intestinal CYP3A Protein Expression. Journal Clinical Investigation 1997; 99(10):2545-2553.



This figure demonstrates the effects of grapefruit juice on felodipine pharmacokinetics and pharmacodynamics.[1] The top graph shows felodipine plasma concentrations at specific time points, up to 24 hours, following administration of a single dose of felodipine with 250 ml of grapefruit juice or water. The bottom graph shows systolic and diastolic blood pressure from the same time points. When felodipine is taken with grapefruit juice, as opposed to water or other juices, there are higher felodipine plasma concentrations, as well as a greater decrease in systolic and diastolic blood pressure. This demonstrates a potentially clinically significant effect of the grapefruit juice-felodipine interaction.

1. Lown KS, Bailey DG, Fontana RJ et al. Grapefruit Juice Increases Felodipine Oral Availability in Humans by Decreasing Intestinal CYP3A Protein Expression. Journal Clinical Investigation 1997; 99(10):2545-2553.

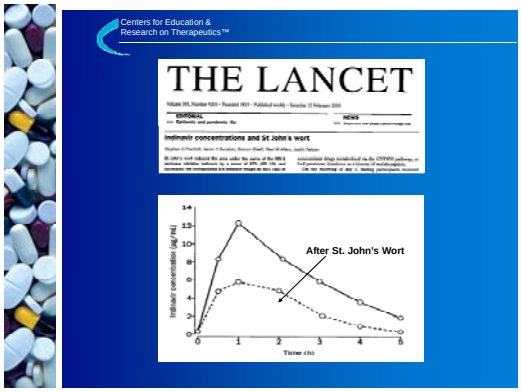
Preventable Adverse Drug Reactions: A Focus on Drug Interactions



Because herbs are foreign to the human body, it has been suspected that herbal remedies could interact with other herbals or even prescription drugs. Investigators have found that ingestion of St. John's wort can result in several clinically significant interactions with drugs that are metabolized by CYP1A2 or CYP3A, including indinavir (Crixivan®)[1] and cyclosporine (Sandimmune® and Neoral®).[2, 3] An interaction with digoxin (Lanoxin®) has also been reported that may be mediated by interference with P-glycoprotein (PGP), a transport system that pumps drugs across membranes discussed in previous slides.[4] These interactions are most likely due to induction of the cytochrome P450 isozyme or the drug transporter, and have caused decreased plasma concentrations of prescription drugs. In the case of cyclosporine, sub-therapeutic levels resulted in transplant organ rejection.

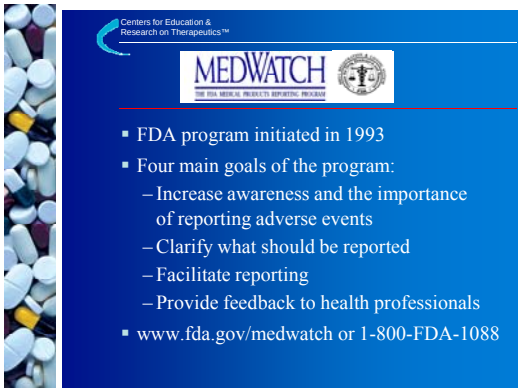
It is likely that many drug-herbal interactions exist but have not yet been detected. It is therefore important that healthcare providers obtain a complete drug history that includes herbal remedies and other natural products and dietary supplements, and that they be alert to potential interactions.

1. Ruschitzka F, Meier PJ, Turina M, Luscher TF, Noll G. Acute heart transplant rejection due to Saint John's wort. Lancet 2000; 355(9203):548-549. **2.** Moss AJ, Hall WJ, Cannom DS et al. Improved survival with an implanted defibrillator in patients with coronary disease at high risk for ventricular arrhythmia. Multicenter Automatic Defibrillator Implantation Trial Investigators [see comments]. N Engl J Med 1996; 335(26):1933-1940. **3.** Breidenbach T, Hoffmann MW, Becker T, Schlitt H, Klempnauer J. Drug interaction of St John's wort with cyclosporin. Lancet 2000; 355(9218):1912. **4.** Johne A, Brockmoller J, Bauer S, Maurer A, Langheinrich M, Roots I. Pharmacokinetic interaction of digoxin with an herbal extract from St John's wort (Hypericum perforatum). Clin Pharmacol Ther 1999; 66(4):338-345.



This slide shows the mean plasma concentration time course of indinavir in eight healthy volunteers with indinavir alone or after taking indinavir with St. John's wort.[1] After administration of St. John's wort, a 57% reduction was observed in the indinavir area under the plasma concentration-time curve (AUC), indicative of reduced exposure to indinavir. This study prompted a public health advisory released by the FDA on February 10, 2000 (www.fda.gov/cder/drug/advisory/stjwort.htm) about the risk of possible drug interactions between St. John's wort and other medications. The potential for loss of therapeutic efficacy due to this interaction supports the importance of taking a complete medication history.

1. Piscitelli SC, Burstein AH, Chaitt D, et al. Indinavir concentrations and St. John's wort. The Lancet 2000; 355(9203):547-48



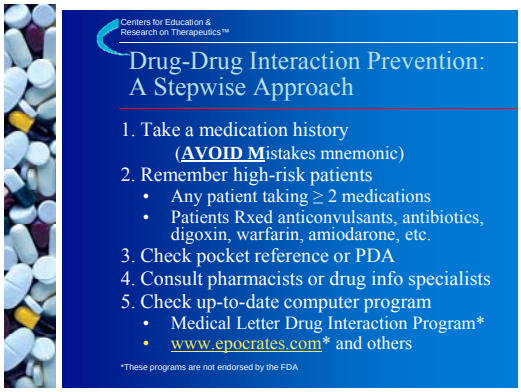
In response to a call for improved post-marketing surveillance of new drugs, MedWatch, the FDA Medical Products Reporting Program, was established in 1993.[1] The program has four general goals. The first goal is to increase awareness of drug, device and other medical product induced disease and the importance of reporting.

The second goal of MedWatch is to clarify what should (and should not) be reported. Health professionals are asked to limit reporting to serious adverse reactions. This is important both in improving the quality of individual reports and enabling the FDA and the manufacturer to focus on the most significant reactions. Proof of causality is not a prerequisite for reporting; suspicion that a medical product may be related to a serious reaction is sufficient reason to report.

The third goal is to make it as easy as possible to report to the FDA. Reports can be submitted in several ways and completion of only one reporting form is necessary. The postage-paid form for voluntary reporting is available in the back of the Physician's Desk Reference or from the FDA via the toll free number (1-800-FDA-1088) or from the FDA/MedWatch website (www.fda.gov/medwatch).

The fourth and final goal of the program is to provide feedback to health professionals about new safety problems with pharmaceuticals and medical devices. Safety-related labeling changes, "Dear Healthcare Professional" correspondence, safety alerts and FDA public health advisories are posted on the FDA/MedWatch website.

1. Kessler DA. Introducing MEDWatch: A new approach to reporting medication and device adverse effects and product problems. JAMA 1993; 269:2765-2768.



It is impossible to remember all of the drug interactions that can occur. One compendium lists over 300 drugs that are thought to interact with warfarin. It is therefore important to develop a stepwise approach to preventing adverse reactions due to drug interactions.

First, taking a good medication history is essential. The "AVOID Mistakes" mnemonic presented on the next slide can help health care practitioners to develop good habits when performing this task.

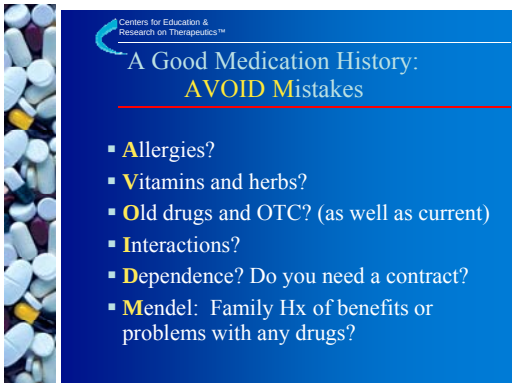
Second, it is essential that physicians develop an understanding of which patients are at risk for drug interactions. Of course, any patient taking two or more medications is at some risk. Studies show that the rate of adverse drug reactions increases exponentially in patients taking four or more medications.[1] Importantly, some categories of drugs are especially at high risk for interactions. These categories include anticonvulsants, antibiotics, and certain cardiac drugs such as digoxin, warfarin, and amiodarone.

Third, any time a patient is taking multiple drugs, we recommend that the first step be to check a readily available pocket reference, recognizing that the interaction may not be listed and a more complete search may be required. We recommend the list available from www.drug-interactions.com.

Fourth, consult other members of the health care team. Depending upon the practice setting, this may be a hospital pharmacist, a Drug Information Center, a specially trained office staff nurse or the nearby pharmacist in community practice.

Fifth, use one of the several computerized databases available. Up- to-date databases are maintained by gsm.com, epocrates.com, and many others. Many of these can be placed on a hand-held computer and can be configured to automatically update each time you synchronize with the desktop computer. Also, the Medical Letter Drug Interaction Program is inexpensive and updated quarterly.

1. Jacubeit T, Drisch D, Weber E. Risk factors as reflected by an intensive drug monitoring system. Agents Actions Suppl 1990; 29:117-125.



Finally, use of the "AVOID Mistakes" mnemonic can help to develop good practice habits and offers a useful way of remembering the components of a good drug history.

A – Allergies: Many patients do not know the correct definition of allergy and will report allergies to medications that caused nausea or another adverse effect unlikely to be related to allergy. Health care providers should try to verify the nature of any reaction reported as allergic. Many patients forget allergic reactions that occur earlier in life.

V – Vitamins: Many patients do not consider vitamins, hormones or oral contraceptives to be medications and may not report them unless specifically asked. As discussed earlier, many patients do not wish to report dietary supplements that they are taking, often due to the negative connotation in the way they are asked.

O – Old drugs are those that were taken until recently but which may still be active due to slow clearance or due to their effects on drug metabolism (inhibition or induction).

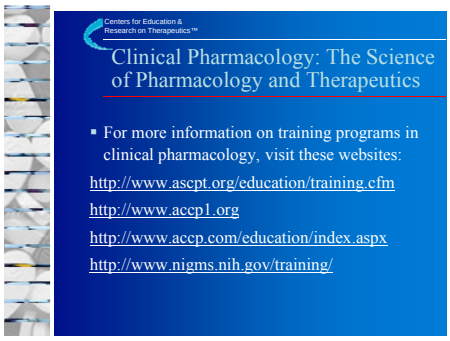
"O" also stands for OTC. Again, unless specifically asked, patients may not report OTC medications that they are taking.

I – Interaction: This is a reminder to ask what happened when medications were combined in the past.

D – Dependence: This refers to the importance of inquiring about drug dependence, obviously with pain medications but also sleep enhancing medications and anti-anxiety medications.

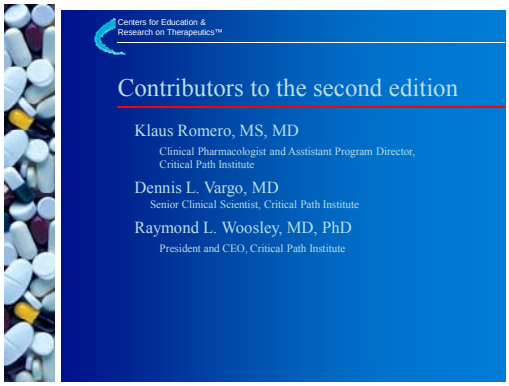
M – Mendel: This is the reminder to consider whether other family members have had similar responses to medications. Many patients will report that they, like a relative, "require high dosages" or "are very sensitive" to all medications. This type of history is not likely to be useful in predicting the individual's response to medicines.

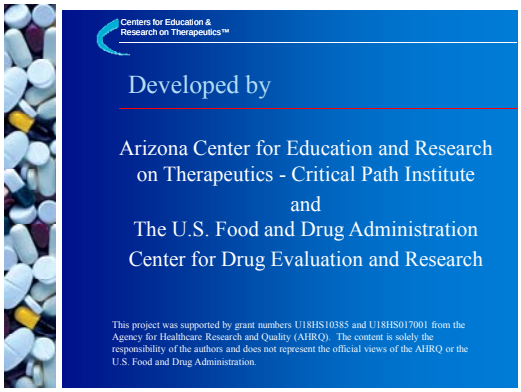

Centers for Education &
Research on Therapeutics™
This completes the ADR learning module.
Please check the following web sites for more learning tools.
www.arizonacert.org (drug interactions)
www.drug-interactions.com
(P450-mediated drug interactions)
www.QTdrugs.org (drug-induced arrhythmia)
www.C-Path.org (drug development)
These web sites are not endorsed by the FDA



Post-doctoral training for physicians and pharmacologists interested in Clinical Pharmacology as a career is available at NIH-sponsored sites as well as other sites throughout the country. For a list of available training programs and contact information, see the website of the American Society for Clinical Pharmacology and Therapeutics (ASCPT), www.ascpt.org, as well as the website of the American College of Clinical Pharmacology, www.accp1.org, and the American College of Clinical Pharmacy, www.accp.com.


Centers for Education &
Research on Therapeutics™
Contributors to the first edition
David A. Flockhart, MD, PhD
Director, Clinical Pharmacology, Indiana University School of Medicine
Sally Yasuda, MS, PharmD
Safety Team Leader, Neurology Products, U.S. Food and Drug Administration
Peter Honig, MD, MPH
Executive Vice-President, Merck Research Laboratories
Curtis Rosebraugh, MD, MPH
Director, Office of New Drugs II, U.S. Food and Drug Administration
Raymond L. Woosley, MD, PhD
President and CEO, Critical Path Institute


Centers for Education &
Research on Therapeutics™
Contributors to the second edition
Klaus Romero, MS, MD
Clinical Pharmacologist and Asstistant Program Director,
Critical Path Institute
Dennis L. Vargo, MD
Senior Clinical Scientist, Critical Path Institute
Raymond L. Woosley, MD, PhD
President and CEO, Critical Path Institute


Centers for Education &
Research on Therapeutics™
Developed by
Arizona Center for Education and Research
on Therapeutics - Critical Path Institute
and
The U.S. Food and Drug Administration
Center for Drug Evaluation and Research
This project was supported by grant numbers U18HS10385 and U18HS017001 from the
Agency for Healthcare Research and Quality (AHRQ). The content is solely the
responsibility of the authors and does not represent the official views of the AHRQ or the
U.S. Food and Drug Administration.