# DRUG INTERACTIONS

## Common Clinical Pitfalls

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There are numerous pitfalls between the reporting of a drug interaction in the medical literature and the successful application of this information to a specific patient. The most obvious mistake is failing to realize that the combination of drugs the patient is receiving can interact in a clinically important way. Perhaps just as common, however, is to be aware that the patient is receiving interacting drugs, but to apply this information inappropriately to the assessment and management of the patient. This often results in an overestimation or underestimation of the clinical importance of the interaction to the patient in question.

**Relying on memory to determine which drugs interact**

***MAO Inhibitor Interactions:*** The infrequent use of MAOI may reduce awareness of potentially serious drug interactions.

- Dextromethorphan: Serotonin syndrome reported.
- SSRIs: Serotonin syndrome, fatalities reported (avoid combination)
- Meperidine (Demerol): Serotonin syndrome reported
- Venlafaxine (Effexor) or nefazodone (Serzone): Serotonin syndrome reported (avoid combinations)
- Decongestants (cold products): fatal hypertensive reactions reported.

**Relying *only* on personal clinical experience to assess the importance of a given drug interaction.**

***Erythromycin + Theophylline:*** Since most patients have no adverse consequences, one can conclude that the combination is *always* safe.

- Tennessee Case: Boy on theophylline developed permanent brain damage following erythromycin
- "I have used theophylline and erythromycin together in 200 patients and have not seen any theophylline toxicity"

***Iron + Thyroid Replacement:*** It took over a century for this interaction to be detected.

- Iron can substantially reduce the absorption of thyroid replacement, resulting in increased TSH and symptoms of hypothyroidism

**Failure to understand the statistics of rare events**

***For an adverse drug interaction that occurs once in 1000 cases:***

- One would need to observe 3000 patients to have a 95% chance of observing the adverse interaction.
- Oral Contraceptives + Antibiotics: Risk of unintended pregnancy probably low, so one would need to study a large number of people to detect the interaction.
- Cisapride (Propulsid) + Clarithromycin (Biaxin): Clarithromycin inhibits the CYP3A4 metabolism of cisapride, but probably most patients would not manifest cardiac arrhythmias. Nonetheless, the combination is contraindicated.

**Failure to consider the effects of dose on the outcome of the interaction.**

***Almost all drug interactions are dose dependent:***

- ***Cimetidine (Tagamet) + Theophylline***
  - Cimetidine 400 mg/day usually increases theophylline levels only slightly, while 800 mg/day or more tend to have larger effects
- ***Fluconazole (Diflucan):***
  - Fluconazole in doses as low as 100 mg/day can inhibit warfarin metabolism (metabolized by CYP2C9)
  - Larger doses of fluconazole (e.g., 200-400 mg/day or more) usually needed to inhibit metabolism of CYP3A4 substrate drugs.
- ***Warfarin + alcohol:***
  - Acute alcohol intoxication may increase INR, but smaller doses have little effect on warfarin response

**Assuming that all members of a drug class will interact in a homogenous manner**

***Very few drug classes interact in a homogeneous way:***

- Non-sedating & "Low-sedating" antihistamines:
  - Astemizole or terfenadine: CYP3A4 inhibitors ➔ arrhythmias
  - citirazine (Zyrtec): Does not appear to be cardiotoxic
  - loratadine (Claritin): Does not appear to be cardiotoxic*
  - fexofenadine (Allegra): Does not appear to be cardiotoxic*

  *CYP3A4 inhibitors may increase serum levels, but no effect on QTc
- Selective serotonin reuptake inhibitors (SSRIs):
  - fluoxetine (Prozac): potent inhibitor of CYP2D6
  - paroxetine (Paxil): potent inhibitor of CYP2D6
  - sertraline (Zoloft): weak inhibitor of CYP2D6
  - citalopram (Celexa): little or no effect on CYP2D6
  - fluvoxamine (Luvox): little or no effect on CYP2D6*

  *But fluvoxamine inhibits CYP3A4 and CYP1A2
- HMG-CoAs ("Statins") + Inhibitors of CYP3A4:
  - lovastatin (Mevacor) ➔ risk of myopathy
  - simvastatin (Zocor) ➔ risk of myopathy
  - pravastatin (Pravachol) ➔ myopathy risk appears minimal
  - fluvastatin (Lescol) ➔ myopathy risk appears minimal
  - atorvastatin (Lipitor) ➔ probably low risk; need more data
  - cerivastatin (Baycol) ➔ probably low risk; need more data

| Drug Class | May Inhibit Metabolism | Unlikely to Inhibit Metabolism |
|---|---|---|
| H2-Blockers | cimetidine (Tagamet) | famotidine (Pepcid)<br>ranitidine (Zantac)<br>nizatidine (Axid) |
| Macrolides | erythromycin (E-Mycin)<br>clarithromycin (Biaxin)<br>troleandomycin (TAO) | azithromycin (Zithromax)<br>dirithromycin (Dynabac)[b] |
| Quinolones | ciprofloxacin (Cipro)<br>enoxacin (Penetrex)<br>grepafloxacin (Raxar)<br>norfloxacin (Noroxin)[a] | trovafloaxacin (Trovan)<br>levofloxacin (Levoquin)<br>lomefloxacin (Maxaquin)<br>ofloxacin (Floxin)<br>sparfloxacin (Zagam) |

a. Norfloxacin is only a weak inhibitor of CYP1A2
b. Based on limited clinical data

**Failure to appreciate the time-course of drug interactions.**

***The same precipitant drug may result in widely varying time to new steady state when added to different object drugs:***

- Cimetidine added to patients stabilized on:
  - theophylline: new steady state theophylline level in 2-3 days
  - warfarin (Coumadin): new steady state INR effect in 7-10 days
  - phenytoin (Dilantin): new steady state phenytoin level in weeks

***Different precipitant drugs may result in varying time to new steady state when added to same object drug.***

- Carbamazepine (Tegretol) + Enzyme Inhibitors (Rapid Toxicity): Most inhibitors result in carbamazepine toxicity within 2-3 days - Verapamil (Calan, Isoptin), Diltiazem (Cardizem), Clarithromycin (Biaxin), Erythromycin, Isoniazid (INH) Cimetidine (Tagamet), Propoxyphene (Darvocet, Darvon)
- Carbamazepine (Tegretol) + Enzyme Inhibitors (Delayed Toxicity): Danazol (Danocrine), Fluoxetine (Prozac) may take 1-2 weeks before carbamazepine toxicity occurs

***Antihypertensives + NSAIDs:***

- NSAIDs tend to reduce the antihypertensive effect, but the effect is usually gradual (taking more than a week) and increase in blood pressure tends to be small (e.g. 5-10 mmHg).

**Failure to consider the effects of sequence of administration on the outcome of the interaction.**

***Titrated Object Drugs:***

- Primary risk is when precipitant drug added to stabilized object drug

***Thyroid + Warfarin (Coumadin):***

- Warfarin started in a patient on stabilized on thyroid: risk of adverse drug interaction minimal
- Thyroid started in a patient stabilized on warfarin: marked increase in hypoprothrombinemic response likely

***Calcium Channel Blockers + Enzyme Inducers:***

- Time course depends upon sequence of administration of the drugs.
  - Calcium channel blocker first: may take 7-10 days
  - Enzyme inducer first: lack of response to CCB seen immediately

**Assuming that separating the doses of the interacting drugs will circumvent absorption interactions**

***Antacids + Quinolones:***

- Reduced absorption of quinolones; effect may be large, so it is best to avoid antacids in patients receiving these drugs; if combination is used, give quinolone at least 2 hours before or 6 hours after antacid.

***Thyroid Hormones + Cholestyramine:***

- Enterohepatic circulation of thyroid hormones may result in interaction regardless of how far apart the cholestyramine is given. This effect has been intentionally to speed elimination of thyroxine in patients with iatrogenic thyrotoxicosis.

**Failure to realize that stopping the precipitant drug can result in an adverse interaction.**

***Carbamazepine (Tegretol) + Theophylline:***

- Baltimore case: Severe theophylline toxicity in boy after carbamazepine stopped (no change in theophylline dose)
- Two physicians involved (apparent lack of communication)

***Warfarin (Coumadin) + Enzyme Inducers:***

- Fatal bleeding episodes reported if enzyme inducer (eg. barbiturate) is stopped without monitoring for increased warfarin response

**Assuming that the magnitude of a drug interaction in your patient will be the same as mean values from clinical studies.**

***Fluconazole (Diflucan) + Warfarin (Coumadin):***

- In 7 patients on warfarin fluconazole produced a mean increase in Pro-Time of about 40%, but range was from 15% to almost 65%

***Cholestyramine + Valproic Acid (Depakene):***

- Cholestyramine binds valproic acid in gastrointestinal tract
- Marked difference in magnitude of effect from person to person

**Assuming that all routes of administration interact in the same way.**

***Calcium Channel Blockers + Enzyme Inducers:***

- Verapamil + rifampin (rifampin markedly reduces first-pass metabolism of verapamil; effect on IV verapamil much less marked)

***Erythromycin + Midazolam (Versed):***

- Marked increase in midazolam serum concentrations after oral midazolam, but effect much smaller with IV midazolam

**Failure to consider pharmacogenetics of patient**

***Paroxetine (Paxil) or Fluoxetine (Prozac) + Desipramine:***

- Paroxetine and fluoxetine inhibit CYP2D6 (which metabolizes desipramine), but poor metabolizers (PMs) do not have the enzyme and thus paroxetine has no effect on desipramine in PMs.

***Codeine ineffective in absence of CYP2D6 activity:***

- Codeine must be converted to morphine by CYP2D6 in order to produce analgesic effects. Hence, codeine is likely to be ineffective in people lacking CYP2D6 (or in those on potent CYP2D6 inhibitors).

**Failure to consider dietary habits of patient**

***Grapefruit Juice Inhibits CYP3A4:***

- Grapefruit juice can double serum levels of felodipine (Plendil)
- Other drugs interacting with grapefruit juice: nifedipine (Procardia), nitrendipine, cyclosporine (Sandimmune), terfenadine (Seldane)
- Any drug metabolized by CYP3A4 may interact

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# CYTOCHROME P450 ENZYMES AND DRUG INTERACTIONS

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Inhibition of cytochrome P450 drug metabolizing isozymes is a relatively common mechanism by which clinically important drug interactions occur. The recommended nomenclature for these enzymes is now "CYP" to designate human cytochrome P450, followed by an Arabic number to designate the P450 family, followed by a capital letter to designate the subfamily; followed by an Arabic number to indicate the individual gene. Thus, examples of individual isozymes would include CYP1A2, CYP2C9, CYP2D6, etc. Some important characteristics of cytochrome P450 isozymes include the following:

- Inhibition is substrate independent (that is, a potent inhibitor of CYP3A4 is *very* likely to inhibit the metabolism of any drug metabolized by CYP3A4)
- Some substrates are also inhibitors for the same enzyme, perhaps due to competitive inhibition of enzyme activity. (e.g., omeprazole for CYP2C19 or verapamil for CYP3A4)
- Some inhibitors affect more than one isozyme (e.g., fluvoxamine inhibits CYP1A2, CYP2C19, and CYP3A4).
- The magnitude of inhibition of drug metabolism by cytochrome P450 enzymes tends to be dose related over the dosage range of the inhibitor (e.g., cimetidine 400 mg/day vs. 1200 mg/day)
- An inhibitor may produce inhibition of one isozyme at one dose, but require a larger dose of the inhibitor to inhibit another CYP isozyme (e.g., fluconazole inhibits CYP2C9 at low doses such as 100 mg/day, but inhibition of CYP3A4 requires larger doses such as 200-400 mg/day).
- Some substrates are metabolized by more than one isozyme (e.g., diazepam is metabolized by both CYP2C19 and CYP3A4, phenytoin is metabolized by CYP2C9 and CYP2C19, and tricyclic antidepressants are metabolized by many CYP450 isozymes).
- Most CYP450 isozyme inhibitors are themselves metabolized by the liver, but some are drugs with primarily renal elimination (e.g., cimetidine, fluconazole)
- Enantiomers may be metabolized by different isozymes. For example, the relatively weak anticoagulant R-warfarin is metabolized primarily by CYP1A2, while the more potent S-warfarin is metabolized by CYP2C9. Thus inhibitors of CYP1A2 tend to produce only small increases in the hypoprothrombinemic response to warfarin, while CYP2C9 inhibitors can sometimes produce large increases in warfarin response.

**References:**

1. Bertz RJ, Granneman GR. Use of in vitro and in vivo data to estimate the likelihood of metabolic pharmacokinetic interactions. Clin Pharmacokinet 1997;32:210-258.
2. Levy RH, Bajpai M. Phenytoin: interactions with other drugs: mechanistic aspects, in: Antiepileptic Drugs, 4th Ed., Levy RH, Mattson RH, Meldrum BS (Eds.) Raven Press, New York, 1995)

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

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| Isozyme | Substrates | | | Inhibitors | | Inducers |
|---|---|---|---|---|---|---|
| **CYP1A2** | Caffeine<br>Clomipramine (Anafranil)<br>Clozapine (Clozaril)<br>Flutamide (Enlexin)<br>Imipramine (Tofranil) | Olanzapine (Zypyrexa)<br>Tacrine (Cognex)<br>Theophylline (Theo-Dur)<br>Ropinirole (Requip)<br>R-Warfarin (Coumadin) | Zileuton (Zyflo) | Cimetidine (Tagamet)<br>Ciprofloxacin (Cipro)<br>Enoxacin (Penetrex)<br>Ethinyl Estradiol<br>Fluvoxamine (Luvox) | Isoniazid (INH)<br>Mexiletine (Mexitil)<br>Norethindrone<br>Tacrine (Cognex)<br>Zileuton (Zyflo) | Charcoal-broiled meat<br>Smoking |
| **CYP2C9** | Celecoxib (Celebrex)<br>Diclofenac (Voltaren)<br>Dronabinol (Marinol)<br>Flurbiprofen (Ansaid)<br>Fluvastatin (Lescol)<br>Glimepiride<br>Glipizide (Glucotrol)?<br>Glibenclamide? | Ibuprofen (Motrin)<br>Indomethacin (Indocin)<br>Losartan (Cozaar)<br>Montelukast (Singulair)<br>Naproxen (Naprosyn)<br>Phenytoin (Dilantin)<br>Piroxicam (Feldene)<br>Tolbutamide (Orinase) | Torsemide (Demadex)<br>S-Warfarin (Coumadin)<br>Zafirlukast (Accolate) | Amiodarone (Cordarone)<br>Cimetidine (Tagamet)<br>Clopidogrel (Plavix)<br>Co-trimoxazole (Bactrim)<br>Disulfiram (Antabuse)<br>Efavirenz (Sustiva)<br>Fluconazole (Diflucan)<br>Fluvastatin (Lescol) | Fluvoxamine (Luvox)<br>Isoniazid (INH)<br>Itraconazole (Sporanox)<br>Ketoconazole (Nizoral)<br>Metronidazole (Flagyl)<br>Sulfinpyrazone (Anturane)<br>Ticlopidine (Ticlid)<br>Zafirlukast (Accolate) | Aminoglutethimide (Cytandren)<br>Barbiturates<br>Carbamazepine (Tegretol)<br>Griseofulvin (Fulvicin)<br>Nafcillin (Unipen)<br>Phenytoin (Dilantin)<br>Primidone (Mysoline)<br>Rifampin (Rimactane) |
| **CYP2C19** | Amitriptyline (Elavil)<br>Carisoprodol (Soma)<br>Citalopram (Celexa)<br>Clomipramine (Anafranil<br>Diazepam (Valium) | Imipramine (Tofranil)<br>Lansoprazole (Prevacid)<br>Mephenytoin<br>Pantoprazole (Protonix)<br>Omeprazole (Prilosec) | Pentamidine (Pentam)<br>Phenytoin (minor pathway)<br>Proguanil*<br>Rabeprazole (Aciphex)<br>R-Warfarin (Coumadin) | Efavirenz (Sustiva)<br>Felbamate (Felbatol)<br>Fluconazole (Diflucan)<br>Fluoxetine (Prozac)<br>Fluvoxamine (Luvox) | Omeprazole (Prilosec)<br>Ticlopidine (Ticlid) | |
| **CYP2D6** | Amitriptyline (Elavil)<br>Carvedilol (Coreg)<br>Clomipramine (Anafranil)<br>Codeine* → Morphine<br>Desipramine (Norpramin)<br>Dexfenfluramine (Redux)<br>Dextromethorphan<br>Efavirenz (Sustiva)<br>Encainide<br>Flecainide (Tambocor)<br>Fluoxetine (Prozac) | Fluvoxamine (Luvox)<br>Haloperidol (Haldol)<br>Hydrocodone<br>Imipramine (Tofranil)<br>Maprotiline<br>Methamphetamine<br>Metoprolol (Lopressor)<br>Mexiletine (Mexitil)<br>Nortriptyline (Pamelor)<br>Oxycodone (Percocet) | Paroxetine (Paxil)<br>Perphenazine (Trilafon)<br>Propafenone (Rhythmol)<br>Propranolol (Inderal)<br>Risperidone (Risperdal)<br>Thioridazine (Mellaril)<br>Timolol (Blocadren)<br>Tramadol (Ultram)<br>Trazodone (Desyrel)<br>Venlafaxine (Effexor) | Amiodarone (Cordarone)<br>Chloroquine (Aralen)<br>Cimetidine (Tagamet)<br>Diphenhydramine (Benadryl)<br>Fluoxetine (Prozac)<br>Haloperidol (Haldol)<br>Mibefradil (Posicor)<br>Paroxetine (Paxil)<br>Perphenazine (Trilafon)<br>Propafenone (Rhythmol) | Propoxyphene (Darvon)<br>Quinacrine<br>Quinidine (Quinidex)<br>Quinine<br>Ritonavir (Norvir)<br>Sertraline (Zoloft) (weak)<br>Terbinafine (Lamisil)<br>Thioridazine (Mellaril) | **Note:** CYP2D6 appears relatively resistant to enzyme induction. |
| **CYP3A4** | Alfentanil (Alfenta)<br>Alprazolam (Xanax)<br>Amlodipine (Norvasc)<br>Amiodarone (Cordarone)<br>Astemizole<br>Atorvastatin (Lipitor)<br>Bepridil (Vascor)<br>Bromocriptine (Parlodel)<br>Buspirone (Buspar)<br>Carbamazepine (Tegretol)<br>Cisapride (Propulsid)<br>Citalopram (Celexa)<br>Clarithromycin (Biaxin)<br>Cyclophosphamide<br>Cyclosporine (Neoral) ⊙<br>Dapsone<br>Delavirdine (Rescriptor)<br>Dexamethasone⊙<br>Diazepam (Valium)<br>Diltiazem (Cardizem) ⊙<br>Disopyramide (Norpace)<br>Doxorubicin (Adriamycin)<br>Efavirenz (Sustiva)<br>Ergotamine (Ergomar)<br>Erythromycin (E-Mycin) | Ethinyl Estradiol<br>Etoposide (Vepesid) ⊙<br>Felodipine (Plendil)<br>Fentanyl (Sublimaze)<br>Finasteride (Proscar)<br>Flutamide (Eulexin)<br>Ifosfamide (Ifex)<br>Indinavir (Crixivan)<br>Isradipine (DynaCirc)<br>Itraconazole (Sporanox)<br>Ketoconazole (Nizoral)<br>Lidocaine<br>Loratadine (Claritin)<br>Losartan (Cozaar)<br>Lovastatin (Mevacor)<br>Methadone<br>Methylprednisolone<br>Mibefradil (Posicor)<br>Miconazole (Monistat)<br>Midazolam (Versed)<br>Nefazodone (Serzone)<br>Nicardipine (Cardene) ⊙<br>Nifedipine (Adalat)<br>Nimodipine (Nimotop)<br>Nisoldipine (Sular) | Nitrendipine<br>Paclitaxel (Taxol) ⊙<br>Pimozode (Orap)<br>Prednisolone<br>Quetiapine (Seroquel)<br>Quinidine (Quinidex)<br>Quinine<br>Rifabutin (Mycobutin)<br>Ritonavir (Norvir)<br>Saquinavir (Invirase)<br>Sertraline (Zoloft)<br>Sibutramine (Meridia)<br>Sildenafil (Viagra)<br>Simvastatin (Zocor)<br>Tacrolimus (Prograf) ⊙<br>Tamoxifen (Nolvadex)<br>Terfenadine<br>Testosterone<br>Theophylline (minor pathway)<br>Triazolam (Halcion)<br>Verapamil (Calan) ⊙<br>Vinblastine (Velban) ⊙<br>Vincristine (Oncovin) ⊙<br>R-Warfarin (Coumadin)<br>Zolpidem (Ambien) | Clarithromycin (Biaxin)<br>Cyclosporine (Neoral) ⊙<br>Danazol (Danocrine)<br>Delavirdine (Rescriptor)<br>Diltiazem (Cardizem) ⊙<br>Erythromycin (E-Mycin)<br>Ethinyl Estradiol<br>Fluconazole (Diflucan) (weak)<br>Fluvoxamine (Luvox)<br>Grapefruit juice<br>Indinavir (Crixivan)<br>Isoniazid (INH)<br>Itraconazole (Sporanox)<br>Ketoconazole (Nizoral)<br>Metronidazole (Flagyl)<br>Methylprednisolone<br>Mibefradil (Posicor)<br>Miconazole (Monistat)<br>Nefazodone (Serzone)<br>Nelfinavir (Viracept)<br>Norethindrone<br>Norfloxacin (Norflox)<br>Oxiconazole (Oxistat)<br>Prednisone | Quinidine<br>Quinine<br>Ritonavir (Norvir)<br>Saquinavir (Invirase)<br>Troleandomycin (TAO)<br>Verapamil (Calan) ⊙<br>Zafirlukast (Accolate)<br>Zileuton | Aminoglutethimide (Cytandren)<br>Barbiturates<br>Carbamazepine (Tegretol)<br>Dexamethasone<br>Efavirenz (Sustiva)<br>Glutethimide<br>Griseofulvin (Fulvicin)<br>Nevirapine (Viramune)<br>Phenytoin (Dilantin)<br>Primidone (Mysoline)<br>Rifabutin (Mycobutin)<br>Rifampin (Rimactane)<br>Troglitazone (Rezulin) |

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