

Cytochrome P450 Drug Interactions

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(Last Updated May 2003-See newly added CYP2C8 category on page 4)

The characterization of drug interactions by metabolic pathways is complex. Just because a medication interacts with one substrate of a particular cytochrome P450 pathway, does not mean it affects all substrates of that isozyme. Genetics, age, nutrition, stress, liver disease, hormones, and other endogenous chemicals also influence drug metabolism. Additional influences on drug interactions include drug dosing issues (timing of dose, sequence of administration, route of administration and duration of therapy) and specific drug features (narrow therapeutic index, high extraction ratio, multiple metabolic pathways).

In the table that follows italics denote those substrates, inhibitors, and inducers that have been involved in a drug interaction of clinical relevance using the criteria established in several drug interaction references such as Hansten PD, Horn JR. *Drug Interactions Analysis and Management*. Vancouver, WA: Applied Therapeutics, Inc., 2002 and Tatro DS (ed). *Drug Interaction Facts*. St. Louis, MO: Facts & Comparisons, Inc., 2002. This table is not comprehensive as new information is constantly being identified.

CYP1A2				
-----Substrates-----		-----Inhibitors-----		--Inducers--
acetaminophen <i>amitriptyline</i> caffeine chlordiazepoxide <i>clomipramine</i> clopidogrel <i>clozapine</i> cyclobenzaprine <i>desipramine</i> diazepam estradiol flutamide <i>fluvoxamine</i> <i>haloperidol</i> <i>imipramine</i> levobupivacaine	mexiletine mirtazapine naproxen nortriptyline olanzapine ondansetron propafenone propranolol riluzole <i>ropinirole</i> ropivacaine <i>tacrine</i> <i>theophylline</i> verapamil <i>(R)-warfarin</i> zileuton	amiodarone <i>cimetidine</i> <i>ciprofloxacin</i> citalopram <i>clarithromycin</i> diltiazem <i>enoxacin</i> <i>erythromycin</i> ethinyl estradiol <i>fluvoxamine</i> <i>isoniazid</i> ketoconazole	methoxsalen mexiletine <i>nalidixic acid</i> norethindrone <i>norfloxacin</i> omeprazole <i>oral contraceptives</i> paroxetine tacrine ticlopidine <i>troleandomycin</i> <i>zileuton</i>	<i>carbamazepine</i> charbroiled food lansoprazole omeprazole <i>phenobarbital</i> <i>phenytoin</i> <i>primidone</i> <i>rifampin</i> <i>ritonavir</i> <i>smoking</i> <i>St John's wort</i>
CYP2C9				
-----Substrates-----		-----Inhibitors-----		--Inducers--
amitriptyline carvedilol celecoxib clomipramine desogestrel <i>diazepam</i> diclofenac dronabinol fluoxetine flurbiprofen fluvastatin formoterol glimepiride glipizide glyburide ibuprofen imipramine indomethacin irbesartan losartan	mefenamic acid meloxicam montelukast naproxen nateglinide omeprazole <i>phenytoin</i> piroxicam rosiglitazone sildenafil sulfamethoxazole tolbutamide torsemide valdecoxib valsartan voriconazole <i>(S)-warfarin</i> zafirlukast zileuton	<i>amiodarone</i> <i>chloramphenicol</i> <i>cimetidine</i> clopidogrel cotrimoxazole delavirdine disulfiram efavirenz fenofibrate <i>fluconazole</i> fluorouracil <i>fluoxetine</i> fluvastatin <i>fluvoxamine</i> gemfibrozil imatinib <i>isoniazid</i> itraconazole	ketoconazole leflunomide lovastatin <i>metronidazole</i> modafinil omeprazole paroxetine sertraline sulfonamides ticlopidine <i>voriconazole</i> <i>zafirlukast</i>	<i>aprepitant</i> <i>carbamazepine</i> <i>phenobarbital</i> <i>phenytoin</i> <i>primidone</i> <i>rifampin</i> <i>rifapentine</i>

More . . .

CYP2C19				
-----Substrates-----		-----Inhibitors-----		--Inducers--
amitriptyline carisoprodol cilostazol citalopram clomipramine cyclophosphamide desipramine diazepam esomeprazole formoterol hexobarbital imipramine indomethacin lansoprazole mephobarbital moclobemide	nelfinavir nilutamide omeprazole pantoprazole pentamidine <i>phenytoin</i> progesterone proguanil propranolol rabeprazole teniposide <i>thioridazine</i> tolbutamide voriconazole (<i>R</i>)-warfarin	citalopram delavirdine efavirenz felbamate fluconazole <i>fluoxetine</i> fluvastatin <i>fluvoxamine</i> indomethacin isoniazid ketoconazole	letrozole <i>modafinil</i> <i>omeprazole</i> oxcarbazepine paroxetine sertraline telmisartan ticlopidine <i>topiramate</i> voriconazole	<i>carbamazepine</i> norethindrone <i>phenobarbital</i> <i>phenytoin</i> prednisone rifampin
CYP2D6				
-----Substrates-----		-----Inhibitors-----		--Inducers--
<i>amitriptyline</i> amphetamine <i>atomoxetine</i> bisoprolol carvedilol cevimeline chlorpromazine chlorpropamide clomipramine clozapine <i>codeine</i> cyclobenzaprine <i>desipramine</i> dexfenfluramine <i>dextromethorphan</i> dolasetron <i>donepezil</i> <i>doxepin</i> encainide fenfluramine <i>fentanyl</i> <i>flecainide</i> fluoxetine fluphenazine fluvoxamine formoterol galantamine <i>haloperidol</i> <i>hydrocodone</i>	<i>imipramine</i> lidocaine maprotiline <i>mepredine</i> <i>methadone</i> methamphetamine methoxyamphetamine metoprolol <i>mexiletine</i> mirtazapine morphine <i>nortriptyline</i> olanzapine ondansetron <i>oxycodone</i> paroxetine perphenazine pindolol <i>propafenone</i> <i>propoxyphene</i> propranolol quetiapine risperidone <i>thioridazine</i> timolol tolterodine <i>tramadol</i> <i>trazodone</i> venlafaxine	<i>amiodarone</i> bupropion celecoxib chloroquine chlorpheniramine <i>cimetidine</i> citalopram clomipramine cocaine desipramine diphenhydramine <i>fluoxetine</i> fluphenazine halofantrine haloperidol hydroxychloroquine imatinib levomepromazine methadone moclobemide norfluoxetine <i>paroxetine</i> perphenazine propafenone propoxyphene quinacrine <i>quinidine</i> ranitidine <i>ritonavir</i> <i>sertraline</i> terbinafine <i>thioridazine</i>	carbamazepine ethanol phenobarbital phenytoin primidone rifampin ritonavir <i>St John's wort</i>	

More. . .

CYP3A4

-----Substrates-----		----Inhibitors----		--Inducers--
<i>alfentanil</i>	<i>estrogens, oral</i>	<i>omeprazole</i>	<i>acitretin</i>	<i>aminoglutethimide</i>
<i>almotriptan</i>	<i>contraceptives</i>	<i>ondansetron</i>	<i>amiodarone</i>	<i>aprepitant</i>
<i>alprazolam</i>	<i>ethinyl estradiol</i>	<i>oral</i>	<i>amprenavir</i>	<i>carbamazepine</i>
<i>amitriptyline</i>	<i>ethosuximide</i>	<i>contraceptives</i>	<i>aprepitant</i>	<i>dexamethasone</i>
<i>amiodarone</i>	<i>etonogestrel</i>	<i>oxybutynin</i>	<i>cimetidine</i>	<i>efavirenz</i>
<i>amlodipine</i>	<i>etoposide</i>	<i>paclitaxel</i>	<i>ciprofloxacin</i>	<i>ethosuximide</i>
<i>amprenavir</i>	<i>exemestane</i>	<i>pantoprazole</i>	<i>clarithromycin</i>	<i>garlic supplements</i>
<i>aprepitant</i>	<i>felodipine</i>	<i>pimozide</i>	<i>cyclosporine</i>	<i>glucocorticoids</i>
<i>atorvastatin</i>	<i>fentanyl</i>	<i>pioglitazone</i>	<i>danazol</i>	<i>glutethimide</i>
<i>bepidil</i>	<i>fexofenadine</i>	<i>prednisolone</i>	<i>delavirdine</i>	<i>griseofulvin</i>
<i>bexarotene</i>	<i>finasteride</i>	<i>prednisone</i>	<i>diltiazem</i>	<i>modafinil</i>
<i>bromocriptine</i>	<i>flutamide</i>	<i>progesterone/ progestins</i>	<i>diethyl- dithiocarbamate</i>	<i>nafcillin</i>
<i>budesonide</i>	<i>fluticasone</i>	<i>quetiapine</i>	<i>efavirenz</i>	<i>nevirapine</i>
<i>buprenorphine</i>	<i>fluvestrant</i>	<i>quinidine</i>	<i>erythromycin</i>	<i>oxcarbazepine</i>
<i>buspirone</i>	<i>galantamine</i>	<i>quinine</i>	<i>ethinyl estradiol</i>	<i>phenobarbital</i>
<i>busulfan</i>	<i>haloperidol</i>	<i>rabeprazole</i>	<i>fluconazole</i>	<i>phenytoin</i>
<i>cannabinoids</i>	<i>hydrocodone</i>	<i>repaglinide</i>	<i>fluoxetine</i>	<i>primidone</i>
<i>caffeine</i>	<i>hydrocortisone</i>	<i>rifabutin</i>	<i>flvoxamine</i>	<i>rifabutin</i>
<i>carbamazepine</i>	<i>ifosfamide</i>	<i>rifampin</i>	<i>gestodene</i>	<i>rifampin</i>
<i>cevimeline</i>	<i>imatinib</i>	<i>ritonavir</i>	<i>grapefruit</i>	<i>rifapentine</i>
<i>chlorpheniramine</i>	<i>imipramine</i>	<i>salmeterol</i>	<i>indinavir</i>	<i>St John's wort</i>
<i>cilostazol</i>	<i>indinavir</i>	<i>saquinavir</i>	<i>imatib</i>	
<i>cisapride</i>	<i>isradipine</i>	<i>sertraline</i>	<i>isoniazid</i>	
<i>cialopram</i>	<i>itraconazole</i>	<i>sibutramine</i>	<i>itraconazole</i>	
<i>clarithromycin</i>	<i>ketoconazole</i>	<i>sildenafil</i>	<i>ketoconazole</i>	
<i>clindamycin</i>	<i>lansoprazole</i>	<i>simvastatin</i>		
<i>clomipramine</i>	<i>letrozole</i>	<i>sirolimus</i>		
<i>clonazepam</i>	<i>levobupivacaine</i>	<i>tacrolimus</i>		
<i>clopidogrel</i>	<i>lidocaine</i>	<i>tamoxifen</i>		
<i>cocaine</i>	<i>lopinavir</i>	<i>temazepam</i>		
<i>cyclobenzaprine</i>	<i>loratadine</i>	<i>testosterone</i>		
<i>cyclophosphamide</i>	<i>losartan</i>	<i>tiagabine</i>		
<i>cyclosporine</i>	<i>lovastatin</i>	<i>tolterodine</i>		
<i>dapsone</i>	<i>methadone</i>	<i>toremifene</i>		
<i>delavirdine</i>	<i>methylprednisolone</i>	<i>tramadol</i>		
<i>desogestrel</i>	<i>miconazole</i>	<i>trazodone</i>		
<i>dexamethasone</i>	<i>midazolam</i>	<i>triazolam</i>		
<i>dextromethorphan</i>	<i>mifepristone</i>	<i>trimetrexate</i>		
<i>diazepam</i>	<i>mirtazapine</i>	<i>valdecoxib</i>		
<i>dihydroergotamine</i>	<i>modafinil</i>	<i>verapamil</i>		
<i>diltiazem</i>	<i>mometasone</i>	<i>vinblastine</i>		
<i>disopyramide</i>	<i>montelukast</i>	<i>vincristine</i>		
<i>docetaxel</i>	<i>nateglinide</i>	<i>vinorelbine</i>		
<i>dofetilide</i>	<i>nefazodone</i>	<i>voriconazole</i>		
<i>dolasetron</i>	<i>nelfinavir</i>	<i>(R)-warfarin</i>		
<i>donepezil</i>	<i>nevirapine</i>	<i>zaleplon</i>		
<i>doxorubicin</i>	<i>nicardipine</i>	<i>zileuton</i>		
<i>dronabinol</i>	<i>nifedipine</i>	<i>ziprasidone</i>		
<i>dutasteride</i>	<i>nimodipine</i>	<i>zolpidem</i>		
<i>efavirenz</i>	<i>nisoldipine</i>	<i>zonisamide</i>		
<i>ergotamine</i>	<i>nitrendipine</i>			
<i>erythromycin</i>	<i>norethindrone</i>			
<i>esomeprazole</i>				

More . . .

CYP2C8			
-----Substrates-----		----Inhibitors----	--Inducers--
amiodarone	<i>repaglinide</i>	anastrozole	carbamazepine
benzphetamine	retinoic acid	<i>gemfibrozil</i>	<i>phenobarbital</i>
carbamazepine	retinol	nicardipine	rifabutin
docetaxel	rosiglitazone	quercetin	<i>rifampicin</i>
fluvastatin	tolbutamide	sulfaphenazole	<i>rifampin</i>
isotretinoin	tretinoin	sulfinpyrazone	
<i>paclitaxel</i>	verapamil	trimethoprim	
phenytoin	warfarin		
pioglitazone	zopiclone		

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References

1. Bottorf MB. Distinct drug-interaction profiles for statins. *Am J Health-Syst Pharm* 1999;56:1019-20.
2. Christensen M, Tybring G, Mihara K, et al. Low daily 10-mg and 20-mg doses of fluvoxamine inhibit the metabolism of both caffeine (cytochrome P4501A2) and omeprazole (cytochrome P4502C19). *Clin Pharmacol Ther* 2002;71:141-52.
3. DeSilva KE, Le Flore DB, Marston BJ, Rimland D. Serotonin syndrome in HIV-infected individuals receiving antiretroviral therapy and fluoxetine. *AIDS* 2001;15:1281-5.
4. Dresser GK, Spence JD, Bailey DG. Pharmacokinetic-pharmacodynamic consequences and clinical relevance of cytochrome P450 3A4 inhibition. *Clin Pharmacokinet* 2000;38:41-57.
5. Graham AS. Cytochrome P450 drug interactions. *The Rx consultant*. 1999;VIII:1-8.
6. Flockhart DA, Tanus-Santos JE. Implications of cytochrome P450 interactions when prescribing medication for hypertension. *Arch Intern Med* 2002;162:405-12.
7. Michalets EL. Update: Clinically significant cytochrome P-450 drug interactions. *Pharmacotherapy* 1998;18:84-112.
8. Physicians' Desk Reference Electronic Library. Montvale: Medical Economics Company; 2002.
9. Welage LS, Berardi RR. Evaluation of omeprazole, lansoprazole, pantoprazole, and rabeprazole in the treatment of acid-related diseases. *JAPhA* 2000;40:52-62.
10. Clarke TA, Waskell LA. The metabolism of clopidogrel is catalyzed by human cytochrome P450 3A and is inhibited by atorvastatin. *Drug Metabolism and Disposition* 2003;31:53-9.
11. Wen X, Wang J, Backman JT, et al. Trimethoprim and sulfamethoxazole are selective inhibitors of CYP2C8 and CYP2C9, respectively. *Drug Metabolism and Disposition* 2002;30:631-5.
12. Niemi M, Backman JT, Neuvonen M, et al. Effects of gemfibrozil, itraconazole, and their combination on the pharmacokinetics and pharmacodynamics of repaglinide: potentially hazardous interaction between gemfibrozil and repaglinide. *Diabetologia* 2003;46:347-51.
13. Gidal BE, Maganti R, Sheth RD. Drug interactions: antiepileptics and oral contraceptives. Princeton Media Associates 2003. <http://www.princetonme.com>. (Accessed May 13, 2003).
14. Omiecinski CJ, Rimmel RP, Hosagrahara VP. Concise review of the cytochrome P450s and their roles in toxicology. *Toxicological Sciences* 1999;48:151-6.
15. Ohya K, Nakajima M, Nakamura S, et al. A significant role of human cytochrome P450 2C8 in amiodarone N-deethylation: an approach to predict the contribution with relative activity factor. *Drug Metabolism and Disposition* 2000;28:1303-10.
16. Glazer NB, Cheatham WW. No evidence exists that pioglitazone induces hepatic cytochrome P450 isoform CYP3A4. *BMJ* 2001;322:235.
17. Tredger JM, Stoll S. Cytochromes P450-their impact on drug treatment. *Hospital Pharmacist* 2002;9:167-73.

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