FDA U.S. FOOD & DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION & RESEARCH
OFFICE OF CLINICAL PHARMACOLOGY

SBIA WEBINARS

Health Communications For Optimal Drug Therapy

Examples of Drugs That Interact With CYP Enzymes & Transporter Systems

Joseph A. Grillo, Pharm.D.
Associate Director of Labeling and Health Communication
Office of Clinical Pharmacology (OCP)
Office of Translational Sciences
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

Disclaimer

- The field of metabolic and transporter pharmacology is rapidly evolving, thus websites discussed herein are meant to be a guide and not considered a comprehensive list of all possible interacting drugs and substances (e.g., foods, including dietary supplements).
- Some of these websites contain examples of drugs with CYP enzyme-based and transporter-based interactions but does not include drugs with other mechanisms leading to drug interactions such as:
  - Certain interactions affecting drug absorption (e.g., chelating agents, resin-based binders, interactions, and drugs that change gut pH)
  - Interactions affecting drug plasma protein binding
  - Pharmacodynamic interactions

Impact of Drug Interactions (DIs)

- Unanticipated, unrecognized, or mismanaged DIs are major contributors to preventable morbidity & mortality
  - Estimated to represent 3–5% of preventable in-hospital adverse reactions
- Important contributor to emergency department visits & hospital admissions
  - 26% of total hospital admissions directly due to adverse drug reactions involved a DDI in one study
- Chicago Tribune investigation (2016)
  - Reporters presented pharmacies with prescriptions for drugs that are known to be harmful or even fatal if taken together
  - 52 % of the time the prescriptions were filled without warning

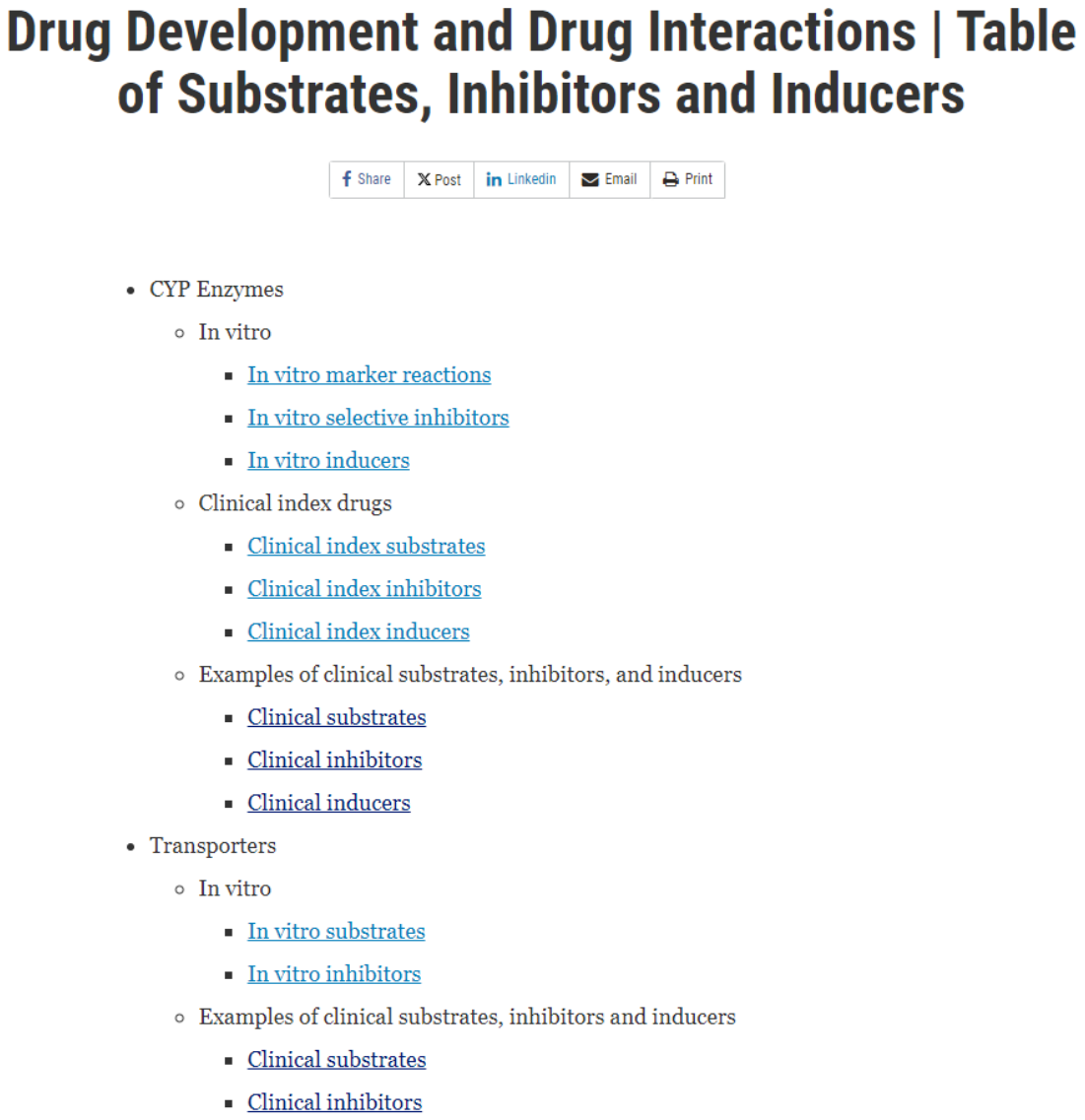
Grillo, J. et al. Clin. Pharmacol. Ther. 105, 1292– 1295 (2019); Leape, L.L. et al. JAMA 274, 35– 43 (1995); Raschetti, R. et al. Eur. J. Clin. Pharmacol. 54, 959– 963 (1999); McDonnell, P.J., et al. Ann. Pharmacother. 36, 1331– 1336 (2002); https://bit.ly/3HEspp9

https://www.fda.gov/drugs/resources-drugs/drug-interactions-what-you-should-know

https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers

https://www.fda.gov/CYPandTransporterInteractingDrugs

Pharmaceutical Industry Focused Site



Drug Development and Drug Interactions | Table of Substrates, Inhibitors and Inducers

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- CYP Enzymes
  - In vitro
    - In vitro marker reactions
    - In vitro selective inhibitors
    - In vitro inducers
  - Clinical index drugs
    - Clinical index substrates
    - Clinical index inhibitors
    - Clinical index inducers
  - Examples of clinical substrates, inhibitors, and inducers
    - Clinical substrates
    - Clinical inhibitors
    - Clinical inducers
- Transporters
  - In vitro
    - In vitro substrates
    - In vitro inhibitors
  - Examples of clinical substrates, inhibitors and inducers
    - Clinical substrates
    - Clinical inhibitors

- Provides tables for drugs commonly used to characterize DI in the in vitro and in vivo dedicated studies as part of drug development
  - Other drugs can be used with appropriate justification
- Also provides clinical examples of drugs for use to characterize DI in other clinical trials

https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers

Requires Hunting For Footnotes

Table 3-2: Examples of clinical inhibitors for CYP-mediated metabolism (for concomitant use clinical DDI studies and/or drug labeling)

	Strong inhibitors	Moderate inhibitors	Weak inhibitors
CYP1A2	ciprofloxacin, enoxacin, fluvoxamine[a]	methoxsalen, mexiletine, oral contraceptives, vemurafenib	acyclovir, allopurinol, cimetidine, peginterferon alpha-2a, piperine, zileuton
CYP2B6	-	-	clopidogrel[b], tenofovir, ticlopidine[c], voriconazole[d]
CYP2C8	gemfibrozil[e]	clopidogrel[b], deferasirox, teriflunomide	trimethoprim
CYP2C9	-	amiodarone[h], fluconazole[f], miconazole, piperine	ceritinib, diosmin, disulfiram, fluvastatin, fluvoxamine[a], voriconazole[d]
CYP2C19	fluconazole[f], fluoxetine[g], fluvoxamine[a], ticlopidine[c]	cenobamate, felbamate, voriconazole[d]	omeprazole
CYP2D6	bupropion, fluoxetine[g], paroxetine, quinidine[h], terbinafine	abiraterone, cinacalcet, duloxetine, lorcaserin, mirabegron, rolapitant	amiodarone[h], celecoxib, cimetidine, clobazam, cobicistat, escitalopram, fluvoxamine[a], labetalol, sertraline, vemurafenib
CYP3A4	The inhibitors below cause a ≥10-fold increase in AUC of sensitive substrate(s): cobicistat[h], danoprevir and ritonavir[j], elvitegravir and ritonavir[j], grapefruit juice[k], indinavir and ritonavir[j], itraconazole[h], ketoconazole[h], lopinavir and ritonavir[h,j], paritaprevir and ritonavir and ombitasvir (and/or dasabuvir)[j], posaconazole, ritonavir[h,j], saquinavir and ritonavir[h,j], tipranavir and ritonavir[j], telithromycin, troleandomycin, voriconazole[d]	aprepitant, ciprofloxacin, conivaptan[l], crizotinib, cyclosporine, diltiazem[m], dronedarone[h], erythromycin[h], fluconazole[f], fluvoxamine[a], grapefruit juice[k], imatinib, isavuconazole, tofisopam, verapamil[h]	chlorzoxazone, cilostazol, cimetidine, clotrimazole, fosaprepitant, istradefylline, ivacaftor, lomitapide, ranitidine, ranolazine[h], ticagrelor[h]
	The inhibitors below cause a 5- to 10-fold increase in the AUC of sensitive substrate(s): ceritinib, clarithromycin[h], idelalisib, nefazodone, nelfinavir	-	-

Footnotes

Note: Strong, moderate, and weak inhibitors are drugs that increase the AUC of sensitive index substrates of a given metabolic pathway ≥5-fold, ≥2 to <5-fold, and ≥1.25 to <2-fold, respectively.

This table provides examples of clinical inhibitors and is not intended to be an exhaustive list. DDI data were collected based on a search of the University of Washington Metabolism and Transport Drug Interaction Database [Hachad et al. (2010), Hum Genomics, 5(1):61].

[a] Strong inhibitor of CYP1A2 and CYP2C19, moderate inhibitor of CYP3A, and weak inhibitor of CYP2D6.
[b] Moderate inhibitor of CYP2C8 and a weak inhibitor of CYP2B6.
[c] Strong inhibitor of CYP2C19 and a weak inhibitor of CYP2B6. The classification as a CYP2B6 inhibitor is based on the AUC change of bupropion. The effect of ticlopidine on hydroxybupropion, which is primarily metabolized by CYP2B6, is larger.
[d] Strong inhibitor of CYP3A, moderate inhibitor of CYP2C19, and weak inhibitor of CYP2B6 and CYP2C9.
[e] Strong inhibitor of CYP2C8 and an inhibitor of OATP1B1 and OAT3.
[f] Strong inhibitor of CYP2C19 and a moderate inhibitor of CYP2C9 and CYP3A.
[g] Strong inhibitors of CYP2C19 and CYP2D6.
[h] Inhibitor of P-gp (, defined as those increasing AUC or Cmax of digoxin, dabigatran, or edoxaban ≥1.5-fold).
[i] Strong inhibitor of CYP3A4 and weak inducer of CYP2B6, CYP2C9, and CYP2C19.
[j] Ritonavir is usually given in combination with other anti-HIV or anti-HCV drugs in clinical practice. Caution should be used when extrapolating the observed effect of ritonavir alone to the effect of combination regimens on CYP3A activities.
[k] The effect of grapefruit juice varies widely among brands and is concentration-, dose-, and preparation-dependent. Studies have shown that it can be classified as a 'strong CYP3A inhibitor' when a certain preparation is used (e.g., high dose, double strength) or as a 'moderate CYP3A inhibitor' when another preparation is used (e.g., low dose, single strength).
[l] The classification is based on studies conducted with intravenously administered conivaptan.
[m] Diltiazem increased the AUC of certain sensitive CYP3A substrates (e.g., buspirone) more than 5-fold.

Abbreviations:
AUC: area under the concentration-time curve; CYP: cytochrome P450; DDI: drug-drug interaction; HIV: human immunodeficiency virus; HCV: hepatitis C virus; OATP1B1: organic anion transporting polypeptide 1B1; OAT3: organic anion transporter 3; P-gp: P-glycoprotein.

HealthCare Provider Focused Site

Filter boxes to find examples of drugs and other substances within selected pathways

Use filters in this box or use the search box ("Search") that is directly below to refine the results.

CYP strong inhibitor: 2C8
CYP moderate inhibitor
CYP weak inhibitor
CYP strong inducer
CYP moderator inducer
CYP weak inducer
CYP sensitive substrate
CYP moderate sensitive substrate
Transporter inhibitor
Transporter substrate
Clear Filters

Search: Export Excel Show 10 entries

Drug or Other Substance	CYP Strg INH	CYP Mod INH	CYP WK INH	CYP Strg IND	CYP Mod IND	CYP WK IND	CYP SENS SUB	CYP Mod SENS SUB	TRNSP INH	TRNSP SUB
gemfibrozil	2C8 strong inhibitor								OAT3; OATP1B1; OATP1B3 inhibitor	

Showing 1 to 1 of 1 entries (filtered from 218 total entries) Previous 1 Next

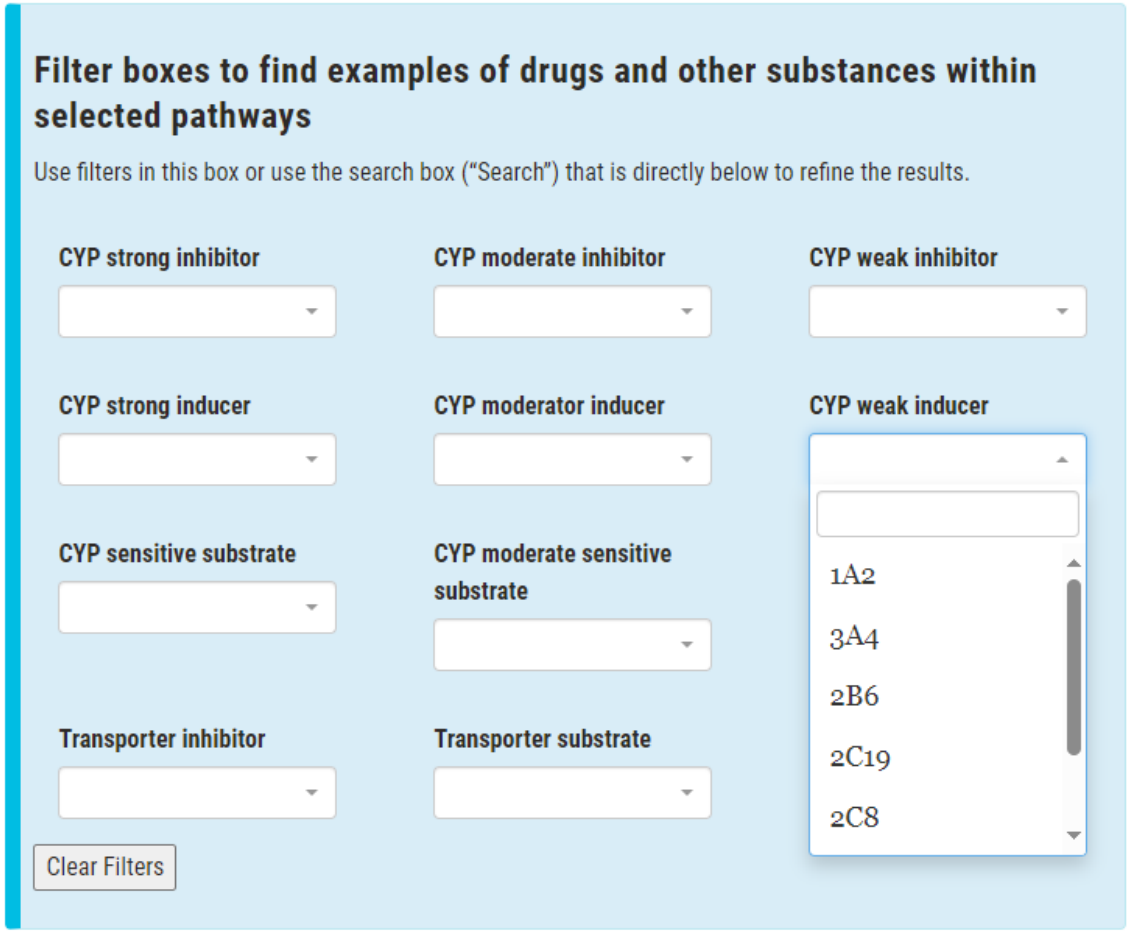
https://www.fda.gov/CYPandTransporterInteractingDrugs

- Searchable
- All relevant information in one table

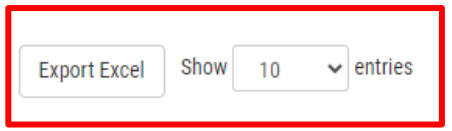
These examples were evaluated and compiled by FDA as an optional resource for healthcare professionals to consult when reviewing information in the DRUG INTERACTIONS section of the approved U.S. Prescribing Information (PI) in clinical practice.

How to Use

Dropdown Filters



Freeform Search



Download results or entire database

How to Optimize Searches

- To refine your search for interacting examples use the filters and/or the search box
- When using the search box…
  - include the name of the drug substance rather than the name of the drug product or the proprietary name
    - e.g., “Atorvastatin” instead of “atorvastatin calcium tablets” or “LIPITOR.”
  - Remember that the search ignores the symbols: ., (,), ‘, -, and /
    - e.g., “St. John’s wort” or “St. John s wort” will return the same result
- The filters and search box operate using an “and” function
  - Use of two or more filters or the combination of filters with the search box returns results that meet both criteria.

Special Situations: Smaller Screens

Drug or Other Substance	CYP Strg INH	CYP Mod INH	CYP WK INH	CYP Strg IND	CYP Mod IND	CYP WK IND
gemfibrozil	2C8 strong inhibitor					

Showing 1 to 1 of 1 entries (filtered from 218 total entries)

Previous 1 Next

Drug or Other Substance	CYP Strg INH	CYP Mod INH	CYP WK INH	CYP Strg IND	CYP Mod IND	CYP WK IND
gemfibrozil	2C8 strong inhibitor					

CYP SENS SUB

CYP Mod SENS SUB

TRNSP INH OAT3; OATP1B1; OATP1B3 inhibitor

TRNSP SUB

How Are We Doing?

- Provide feedback on the quality, clarity, and utility of information provided in these websites at

Email: ocp@fda.hhs.gov

Challenge Question

Which of the following statements is NOT true?

A. The FDA Industry focused DDI website contains separate lists of recommended drugs for use in evaluating CYP enzyme or transporter system effects on a drug in vitro or in vivo as well as clinical examples

B. The majority of drug interactions reported in US drug prescribing information involve CYP enzymes or transporter systems

C. The FDA healthcare provider focused DDI website is a comprehensive list of drugs that effect and are affected by CYP enzymes or transporter systems

D. Drug Interactions are an important contributor to emergency department visits & hospital admissions

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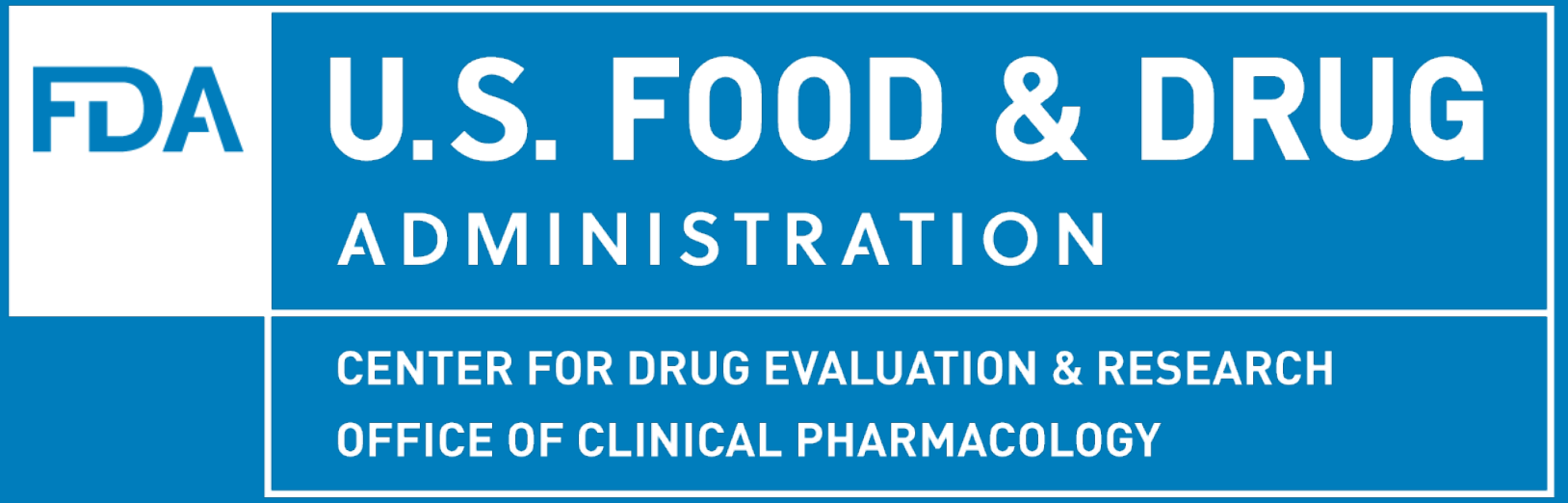
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