Avoiding the Grapefruit Top 5 Drug Interactions All Pharmacists Should Know!

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Disclosure Statement

Vicky Shah has no potential or actual conflicts of interest to disclose

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Learning Objectives

- Identify different interaction types which can lead to subclinical or toxic concentrations
- Recognize major drug interactions in a patient chart
- Discuss appropriate recommendations to correct interactions

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Pre-Test Question 1

True or False

All drug interactions are harmful to patients.

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Pre-Test Question 2

HW is a 59 year old male who presents to your clinic with symptoms of a urinary tract infection. The physician decides to place him on Bactrim for 14 days. His current medications include the following:

- Aspirin
- Omeprazole
- Lisinopril
- Spironolactone

What concerns do you have regarding his medications?

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Pre-Test Question 3

For a patient needing to take a multivitamin and fluoroquinolones, how would you recommend they take the medications?

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Background

3-4% of drug interactions for inpatients are PREVENTABLE

Patients >65 years of age take approximately 7-8 drugs

A drug interaction is a situation in which a substance affects the activity or concentration of a medication, i.e. the effects are increased or decreased, or they produce a new effect that neither produces on its own

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Lazarou J, Pomeranz BH, Corey PN. Incidence of adverse drug reactions in hospitalized patients: a meta-analysis of prospective studies. JAMA. 1998;279:1200–5

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Drug Interactions Are Tough!

You can't memorize them all

You can't prevent them all

You can't predict them all

They can be…

- Beneficial
- Annoying (to the patient and pharmacist)
- Dangerous
- Deadly

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Outcomes of Drug Interactions

- Loss of therapeutic effect
- Toxicity
- Unexpected increase in pharmacological activity
- Beneficial effects (additive and antagonistic effects)
- Chemical or Physical incompatibilities

Lazarou J, Pomeranz BH, Corey PN. Incidence of adverse drug reactions in hospitalized patients: a meta-analysis of prospective studies. JAMA. 1998;279:1200–5

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What are some medications which have narrow therapeutic windows that would require pharmacist monitoring?

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Narrow Therapeutic Window

Aminoglycosides	Carbamazepine	Cyclosporine	Digoxin	Levothyroxine
Lithium	Phenytoin	Tacrolimus	Theophylline	Valproic Acid
		Warfarin		

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Guidance for Industry. Bioavailability and bioequivalence studies for orally administered drug products—general considerations. FDA Center for Drug Evaluation and Research. March 2003. www.fda.gov/cder/guidance/

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Definitions

Synergism	• Therapeutic or toxic effects of two drugs are greater than the effect of individual drug
Additive Effect	• The net effect of two drugs used together is **equal** to the sum of the individual drug effects
Potentiation	• Net effect of two drugs used together is **greater** than the sum of the individual drug effects

Stockley's Interaction Alerts. The Pharmaceutical Press; 2006.

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Definitions

- Antagonism – Effect of one drug can be reduced or abolished by the presence of another drug
  - Chemical – Drug antagonizes the effect of another drug by simple chemical reaction without action on the receptor
    - Acid suppressors
  - Physiological – Effect of a drug is antagonized by another drug by acting on two different types of receptors
    - Acetylcholine and adrenaline
  - Pharmacological – Drug antagonizes the effect of another drug by acting on the same receptor and blocking the drug from binding
    - Beta Blockers and albuterol

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Stockley's Interaction Alerts. The Pharmaceutical Press; 2006.

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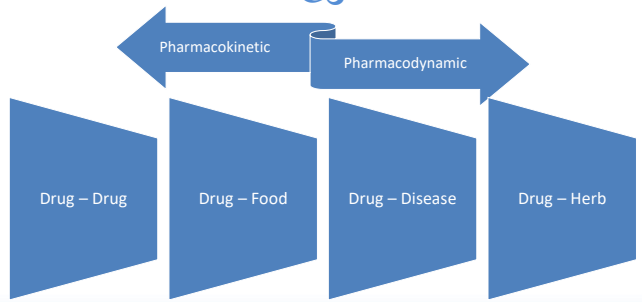
Type of Interactions



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Stockley's Interaction Alerts. The Pharmaceutical Press; 2006.

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Drug Interaction 1

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- JF is a 39 year old male who presents to your pharmacy for a normal brown bag review. He states that he is not in any acute distress at this time and just wants a review of his medications. JF smokes 1 pack per day but denies and drug or alcohol use. JF has a normal diet but has recently been trying new diet fads such as low carb diets and the Hollywood diet. Below are his medications:
  - Clopidogrel
  - Simvastatin
  - Omeprazole
  - Aspirin
  - Theophylline
  - Amiodarone
- What concerns do you have regarding his medications?

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Concerns!

- Clopidogrel + Omeprazole
- Simvastatin + Amiodarone
- Theophylline + Smoking
- Simvastatin + Grapefruit

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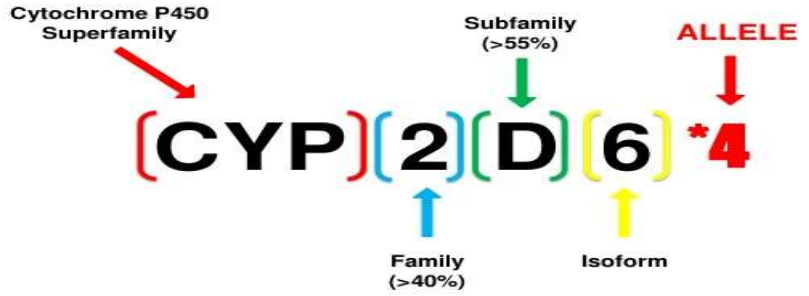
CYP450 Nomenclature



Quinn DI, Day RO. Clinically important drug interactions. In: Speight TM, Holford HG, editors. Avery's Drug Treatment. Auckland: Adis International; 1997. pp. 301–38.

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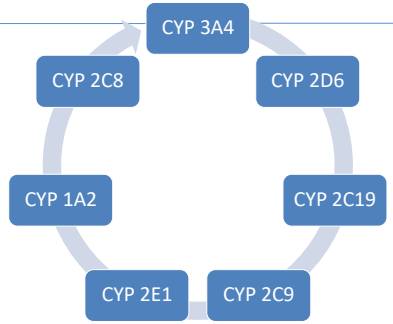
CYP450 Isoenzymes



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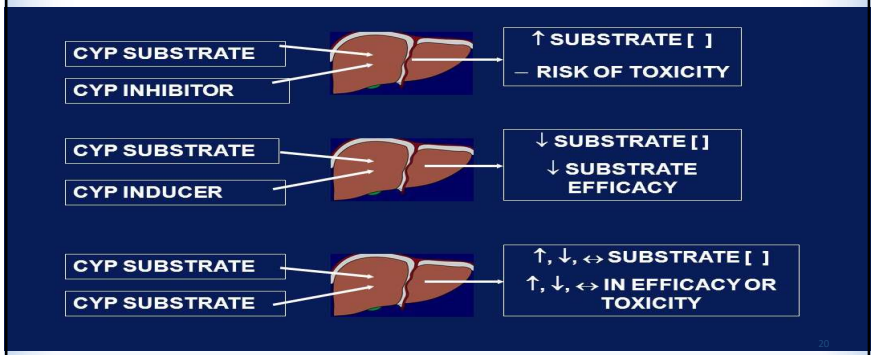
Drug Interactions



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FDA Definitions

Inhibitors work within 1-2 days but inducers may take about 2-4 weeks to see interaction

Term	Inducers	Inhibitors
Strong	>80% decrease in AUC	> 5-fold increase in AUC
Moderate	50-80% decrease in AUC	2-5 fold increase in AUC
Weak	20-50% decrease in AUC	1.25-2 fold increase in AUC

Zhang, Lei, et al. "Predicting drug–drug interactions: an FDA perspective." *The AAPS journal* 11.2 (2009): 300-306.

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CYP Substrates

CYP 1A2	• Caffeine, Theophylline
CYP 2C9	• Ibuprofen, Phenytoin, Warfarin
CYP 2C19	• Omeprazole
CYP 2D6	• Clozapine, Codeine, Metoprolol, Tricyclic Antidepressants
CYP 2E1	• Alcohol
CYP 3A4	• Cyclosporine, Erythromycin, Estrogen, Statins, Phenytoin, Diltiazem, Verapamil, Warfarin, Tacrolimus

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What are some common inducers?

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CYP Inducers

Barbie's	• Barbiturates
Car	• Carbamazepine
Seriously	• Smoking • St. John's Wort
Always	• Alcohol (Chronic Use)
Goes	• Griseofulvin
Really	• Rifampin
PHast	• Phenytoin

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What are some common inhibitors?

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CYP Inhibitors

G	• Grapefruit Juice
F	• Fluoroquinolones
P	• Protease Inhibitors
A	• Azoles
C	• Cimetidine
M	• Macrolides
A	• Amiodarone
N	• Non-DHP CCB

S	• Sodium Valproate
I	• Isoniazid
C	• Cimetidine
K	• Ketoconazole
F	• Fluconazole
A	• Alcohol (Intoxication)
C	• Chloramphenicol
E	• Erythromycin
S	• Sulfonamides
C	• Ciprofloxacin
O	• Omeprazole
M	• Metronidazole

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Clinical Significant Interactions

- Oral Contraceptives + Carbamazepine
- Cyclosporine + Itraconazole
- Amlodipine + Grapefruit juice
- Simvastatin + Protease Inhibitor
- Clopidogrel + Omeprazole

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Clinical Significant Interactions

- Oral Contraceptives + Carbamazepine (inducer)
  - Concentration of OC is reduced by 15-30%
  - Utilize another form of contraception
- Cyclosporine + Itraconazole
- Amlodipine + Grapefruit juice
- Simvastatin + Protease Inhibitor
- Clopidogrel + Omeprazole

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Clinical Significant Interactions

Oral Contraceptives + Carbamazepine (inducer)
- Concentration of OC is reduced by 15-30%
- Utilize another form of contraception

Cyclosporine + Itraconazole (inhibitor)
- Monitor levels of cyclosporine
- Use an alternative agent

Amlodipine + Grapefruit juice (inhibitor)

Simvastatin + Protease Inhibitor

Clopidogrel + Omeprazole

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Clinical Significant Interactions

Oral Contraceptives + Carbamazepine (inducer)
- Concentration of OC is reduced by 15-30%
- Utilize another form of contraception

Cyclosporine + Itraconazole (inhibitor)
- Monitor levels of cyclosporine
- Use an alternative agent

Amlodipine + Grapefruit juice (inhibitor)
- Decrease amlodipine dose by 50%
- Drink orange juice

Simvastatin + Protease Inhibitor

Clopidogrel + Omeprazole

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Clinical Significant Interactions

Oral Contraceptives + Carbamazepine (inducer)
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Cyclosporine + Itraconazole (inhibitor)
- Monitor levels of cyclosporine
- Use an alternative agent

Amlodipine + Grapefruit juice (inhibitor)
- Decrease amlodipine dose by 50%
- Drink orange juice

Simvastatin + Protease Inhibitor (inhibitor)
- AVOID USE!

Clopidogrel + Omeprazole

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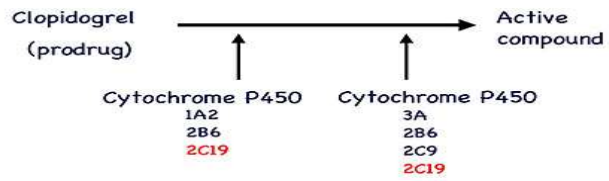
Clinical Significant Interactions



Omeprazole & Esomeprazole → Inhibitors of CYP 2C19
Switch to Pantoprazole

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Drug Interaction 2

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- TR is a 45 year old female who presents with an acute gout attack. She is initiated on colchicine but has no relief of symptoms after 24 hours. The medical resident comes to you to ask what could be happening. You review TR's medication list and realize why she has not felt any relief. What is wrong with her medications?
  - Colchicine
  - Phenytoin
  - Digoxin
  - Verapamil
- What interaction is occurring with Colchicine?
- What other drug interactions are concerning?

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Concerns!

- Colchicine + Phenytoin
- Digoxin + Verapamil
- Verapamil + Phenytoin

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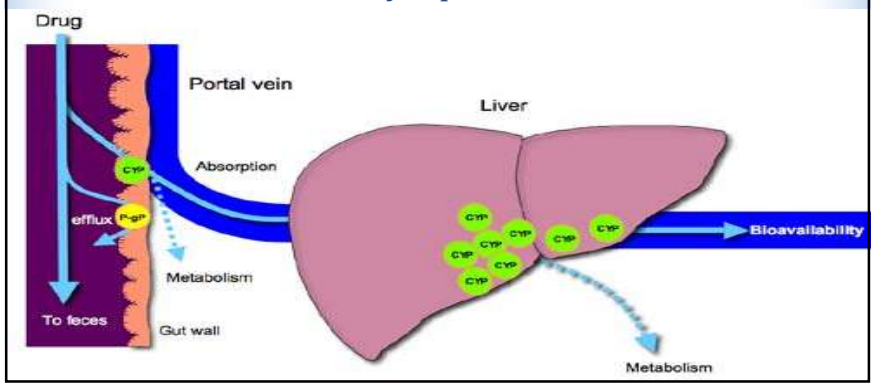
P-Glycoprotein



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P-Glycoprotein

- Efflux transporters
- Found in the gut, gonads, kidneys, biliary systems and brain
- Protects body from harmful substances
- Confusing when a drug is affected by both P-gp and CYP system

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Quinn DI, Day RO. Clinically important drug interactions. In: Speight TM, Holford HG, editors. Avery's Drug Treatment. Auckland: Adis International; 1997. pp. 301–38.

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P-Glycoprotein

Substrates	Inhibitors	Inducers
Colchicine	Azole Antifungals	Rifampin
Dabigatran	Verapamil	Carbamazepine
Cyclosporine	Macrolides	Phenytoin
Digoxin	Protease Inhibitors	St. John's Wort
Rivaroxaban	Amiodarone	
Saxagliptin	Quinidine	
Tacrolimus		

Quinn DI, Day RO. Clinically important drug interactions. In: Speight TM, Holford HG, editors. Avery's Drug Treatment. Auckland: Adis International; 1997. pp. 301–38.

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Drug Interaction 3

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- PW is a 64 year old male with a past medical history of atrial fibrillation requiring long-term use of warfarin. He has tried other oral anticoagulants and has failed therapy. He presents to the pharmacy complaining of bleeding gums and blood seen while urinating. He has not had his INR tested in nearly two months and his previous result was on the higher end of the desired range. Below are his other medications:
  - Fluoxetine
  - Ciprofloxacin
  - Aspirin
  - Fish Oil
  - Omeprazole
  - Ibuprofen
  - Valproic Acid
  - Digoxin
- What concerns do you have regarding his medications?

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Concerns!

- Warfarin + Fluoxetine + Aspirin + Fish Oil + Ibuprofen
- Warfarin + Ciprofloxacin
- Warfarin + Valproic Acid
- Warfarin + Valproic Acid + Digoxin

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What other medications can increase bleed risk for patients?

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Medications Which Increase Bleed Risk

- Warfarin
- Aspirin
- Fish Oil (Doses > 4grams)
- NSAIDs
- Heparin/Lovenox
- Oral Anticoagulants
- Acetaminophen
- Clopidogrel
- SSRIs

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Chen YF, Avery AJ, Neil KE, Johnson C, Dewey ME, Stockley IH. Incidence and possible causes of prescribing potentially hazardous/contraindicated drug combinations in general practice. Drug Saf. 2005;28:67–80.

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Highly Protein Bound

- Warfarin
- Valproic Acid
- Phenytoin
- Digoxin

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Drug Interaction 4

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- HW is a 59 year old male who presents to your clinic with symptoms of a urinary tract infection. The physician decides to place him on Bactrim for 14 days. His current medications include the following:
  - Aspirin
  - Omeprazole
  - Lisinopril
  - Spironolactone
- What concerns do you have regarding his medications?

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Concerns!

Bactrim + Spironolactone + Lisinopril

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What other medications can increase potassium levels?

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Medications Which Lead to Hyperkalemia

- Bactrim
- Spironolactone
- ACE Inhibitors
- Angiotensin Receptor Blockers
- Potassium Supplements
- Oxybutynin
- Heparin/Lovenox
- Cyclosporine
- Tacrolimus
- Triamterene

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Drug Interaction 5

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- NT is a 57 year old male who was recently diagnosed with community acquired pneumonia with a history of COPD. The physician initiated NT on Levofloxacin 500mg daily for 5 days. After completing his 5 day therapy, NT returns stating that he still has ongoing symptoms of pneumonia. The physician asks you to review his medications to determine if his other medications need to be taken into consideration. NT's other medications include:
  - Lisinopril
  - Multivitamin
  - Calcium/Vitamin D
  - Alendronate
  - Metoprolol Tartrate
  - Ferrous Sulfate
- Which medications are concerning?

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Concerns!

- Fluoroquinolones + Multivitamin
- Fluoroquinolones + Calcium
- Fluoroquinolones + Iron Supplements

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Chelation

Tetracyclines and Fluoroquinolones chelate to iron, calcium, magnesium, aluminum, etc.

- Absorption is decreased of antibiotics

Separate by 2-4 hours to ensure sufficient absorption of antibiotics

Educate on not taking antibiotic with milk products

Quinn DI, Day RO. Clinically important drug interactions. In: Speight TM, Holford HG, editors. Avery's Drug Treatment. Auckland: Adis International; 1997. pp. 301–38.

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Common Drug Interactions

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Interaction	Potential effect	Time to effect	Recommendations and comments
Warfarin (Coumadin) *plus* ciprofloxacin (Cipro), clarithromycin (Biaxin), erythromycin, metronidazole (Flagyl) or trimethoprim-sulfamethoxazole (Bactrim, Septra)	Increased effect of warfarin	Generally within 1 week	Select alternative antibiotic.
Warfarin *plus* acetaminophen	Increased bleeding, increased INR	Any time	Use lowest possible acetaminophen dosage and monitor INR.
Warfarin *plus* acetylsalicylic acid (aspirin)	Increased bleeding, increased INR	Any time	Limit aspirin dosage to 100 mg per day and monitor INR.
Warfarin *plus* NSAID	Increased bleeding, increased INR	Any time	Avoid concomitant use if possible; if coadministration is necessary, use a cyclooxygenase-2 inhibitor and monitor INR.
Fluoroquinolone *plus* divalent/trivalent cations or sucralfate (Carafate)	Decreased absorption of fluoroquinolone	Any time	Space administration by 2 to 4 hours.
Carbamazepine (Tegretol) *plus* cimetidine (Tagamet), erythromycin, clarithromycin or fluconazole (Diflucan)	Increased carbamazepine levels	Generally within 1 week	Monitor carbamazepine levels.
Phenytoin (Dilantin) *plus* cimetidine, erythromycin, clarithromycin or fluconazole	Increased phenytoin levels	Generally within 1 week	Monitor phenytoin levels.
Phenobarbital *plus* cimetidine, erythromycin, clarithromycin or fluconazole	Increased phenobarbital levels	Generally within 1 week	Clinical significance has not been established. Monitor phenobarbital levels.

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Phenytoin (Dilantin) *plus* cimetidine, erythromycin, clarithromycin or fluconazole	Increased phenytoin levels	Generally within 1 week	Monitor phenytoin levels.
Phenobarbital *plus* cimetidine, erythromycin, clarithromycin or fluconazole	Increased phenobarbital levels	Generally within 1 week	Clinical significance has not been established. Monitor phenobarbital levels.
Phenytoin *plus* rifampin (Rifadin)	Decreased phenytoin levels	Generally within 1 week	Clinical significance has not been established. Monitor phenytoin levels.
Phenobarbital *plus* rifampin	Decreased phenobarbital levels	Generally within 1 week	Monitor phenobarbital levels.
Carbamazepine *plus* rifampin	Decreased carbamazepine levels	Generally within 1 week	Clinical significance has not been established. Monitor carbamazepine levels.
Lithium *plus* NSAID or diuretic	Increased lithium levels	Any time	Decrease lithium dosage by 50% and monitor lithium levels.
Oral contraceptive pills *plus* rifampin	Decreased effectiveness of oral contraception	Any time	Avoid if possible. If combination therapy is necessary, have the patient take an oral contraceptive pill with a higher estrogen content (>35 µg of ethinyl estradiol) or recommend alternative method of contraception.
Oral contraceptive pills *plus* antibiotics	Decreased effectiveness of oral contraception	Any time	Avoid if possible. If combination therapy is necessary, recommend use of alternative contraceptive method during cycle.

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Sildenafil (Viagra) *plus* nitrates	Dramatic hypotension	Soon after taking sildenafil	Absolute contraindication.
Sildenafil *plus* cimetidine, erythromycin, itraconazole or ketoconazole	Increased sildenafil levels	Any time	Initiate sildenafil at a 25-mg dose.
HMG-CoA reductase inhibitor *plus* niacin, gemfibrozil (Lopid), erythromycin or itraconazole	Possible rhabdomyolysis	Any time	Avoid if possible. If combination therapy is necessary, monitor the patient for toxicity.
Lovastatin (Mevacor) *plus* warfarin	Increased effect of warfarin	Any time	Monitor INR.
SSRI *plus* tricyclic antidepressant	Increased tricyclic antidepressant level	Any time	Monitor for anticholinergic excess and consider lower dosage of tricyclic antidepressant.
SSRI *plus* selegiline (Eldepryl) or nonselective monoamine oxidase inhibitor	Hypertensive crisis	Soon after initiation	Avoid.
SSRI *plus* tramadol (Ultram)	Increased potential for seizures; serotonin syndrome	Any time	Monitor the patient for signs and symptoms of serotonin syndrome.
SSRI *plus* St. John's wort	Serotonin syndrome	Any time	Avoid.
SSRI *plus* naratriptan (Amerge), rizatriptan (Maxalt), sumatriptan	Serotonin syndrome	Possibly after initial dose	Avoid if possible. If combination therapy is necessary, monitor the patient for signs and symptoms

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Resources for Pharmacists

Texts

- Hansten's
- Drug Interaction Facts
- Stockley's Drug Interaction

Online Databases

- Lexicomp
- Micromedex
- Facts and Comparisons
- Clinical Pharmacology
- Dynamed

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What Questions Do You Have?

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