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Avoiding drug interactions: Here's help

You can't count on an electronic prescribing system to catch all potential drug-drug interactions. These at-a-glance tables will help you minimize risk.

PRACTICE RECOMMENDATIONS

- › Be sure to inquire about over-the-counter drugs, herbal remedies, vitamins, and supplements when taking a medication history. **(A)**
- › Use an electronic prescribing software system that flags potential drug-drug interactions. **(A)**
- › Consider adjusting a dosing regimen or temporarily discontinuing a maintenance medication if the drug you are about to prescribe is likely to interact with another agent the patient is taking (and there are no alternatives you can prescribe). **(B)**

Strength of recommendation (SOR)

- (A)** Good-quality patient-oriented evidence
- (B)** Inconsistent or limited-quality patient-oriented evidence
- (C)** Consensus, usual practice, opinion, disease-oriented evidence, case series

CASE▶ John L, a 63-year-old man taking lovastatin (40 mg/d) and ramipril (5 mg/d) for hypercholesterolemia and arterial hypertension was hospitalized with atrial fibrillation. Three days later, he was discharged, with a prescription for amiodarone (200 mg/d). After a month, he was readmitted to the hospital with dark urine and intensifying thigh weakness and achiness. Laboratory testing revealed aspartate aminotransferase and alanine aminotransferase levels 10 times the upper limit of normal, and elevated urine and serum myoglobin.

Drug-drug interactions (DDIs) like the one John experienced between lovastatin and amiodarone are a common cause of readmissions, as well as emergency department visits and hospitalizations, for everything from myopathy to electrolyte imbalance, gastrointestinal (GI) bleeding, hepatotoxicity, renal dysfunction, and changes in blood pressure and heart rate.¹⁻³

Yet many, if not most, DDIs can be avoided. With diligence and the right tools, you can do much to reduce the incidence of such interactions and adverse outcomes.

Polypharmacy and age pose the highest risks

The more medications a patient is taking, of course, the greater the likelihood of a clinically significant DDI. According to 1 study, 13% of patients taking 2 drugs develop a DDI; the incidence approaches 40% for patients taking 5 drugs, and exceeds 80% for patients taking 7 or more medications.⁴

In addition to polypharmacy, age alone is a key risk factor for DDIs.⁵ Pharmacokinetics and pharmacodynamics are frequently altered in older people, who may have slower intestinal transit time; diminished absorption capacity; decreased liver metabolism, mitochondrial function, and renal excretion; and alterations in volemia and body fat distribution.⁶ Although the speed at which these changes occur var-



ies, aging is associated with a progressive deficiency in the regulation of most homeostatic mechanisms and an altered response to receptor stimulation.⁷

Whether age, multiple medications, or both are to blame, the impact on the elderly is striking. One recent retrospective study found 25% of elderly outpatients to be at risk for DDIs.⁸

■ **Very young patients** (<5 years) are also at risk for DDIs because of the immaturity of their enzymatic metabolic system.^{5,9,10} Additional risk factors, detailed in **TABLE 1**, include the presence of an infection or other acute medical condition, a metabolic or endocrine disorder, and taking 1 or more drugs with a narrow therapeutic range. Women are also at higher risk for DDIs than their male counterparts, the result of a slower metabolic capacity and interference with sex hormones.^{3-5,8,9} Pharmacogenetics may also play a big part in DDIs, and more and more studies are focusing on identifying patients at greatest risk.

Lack of coordinated care also increases risk

Another risk factor involves the use of multiple providers.⁹ A woman may be treated by—and

receive prescriptions from—an endocrinologist, a gynecologist, and a family physician (FP), for instance, and get medications from a local pharmacy, a nationwide discount chain, and a mail order pharmacy. As with the number of medications being taken, the greater the number of health care professionals a patient sees, the higher the risk.

To mitigate the risk, encourage your patients to fill all their prescriptions at the same pharmacy—and for your part, take a complete medication history before writing a new prescription.

Medication history in doubt? Schedule a “brown bag review”

Ask patients to provide the name and dose of every medication they’re taking. Inquire specifically about over-the-counter (OTC) cough and cold remedies and complementary and alternative medicines, including herbal remedies, vitamins, and supplements. Patients often neglect to mention nonprescription remedies and may not even think of them as medicine, but OTC products with the potential to interact adversely with prescription drugs may otherwise remain undetected.¹¹⁻¹³

Consider a “brown bag review” for pa-



INSTANT POLL QUESTION

Do you override drug interaction alerts on an electronic prescribing software system?

- Frequently
- Occasionally
- Rarely or never
- I do not use electronic prescribing systems
- Other _____

Go to jfponline.com and take our instant poll

TABLE 1

Risk factors for drug-drug interactions^{3-5,8,9}

Risk factor	Potential result
Acute medical condition (eg, dehydration, infection, alcoholism)	Augmented risk of elevated plasma drug concentration, increased catabolism, inhibition of hepatic drug metabolism
Age (very young [<5 years] and elderly)	Reduced metabolic capacity (greater accumulation of drugs)
Decreased renal and/or hepatic function	Decreased drug clearance/elimination; greater accumulation of drugs or their metabolites
Drug(s) with narrow therapeutic range	Increased risk for dose-related side effects
Female sex	Reduced metabolic capacity, interference with sex hormones
Metabolic or endocrine conditions (eg, fatty liver, obesity, hypothyroidism)	Altered hepatic metabolism, increased body distribution volumes, augmented risk of accumulation for hydrophobic molecules
Polypharmacy (≥ 3 medications)	Increased risk of metabolic and/or pharmacodynamic interference
Pharmacogenetics	Altered metabolic capacity (greater accumulation of drugs or their metabolites)

➤ Consider a “brown bag review”; ask patients to put all their meds in a brown bag and bring them along on their next visit.

tients who don’t know what dosage they’re taking or have difficulty identifying the drugs other physicians have prescribed. Ask them to put all their medications in a brown bag and bring them in on their next visit.^{14,15}

Steps to take to reduce risk

Software systems. A number of free and low-cost software systems identify potential DDIs (See “Check for drug interactions: Software programs to consider” on page 326). While such electronic programs can indeed lower the risk,¹⁶⁻¹⁸ they cannot be counted on to detect or avert every possible adverse interaction.

■ **The downside.** One problem is that some software programs fail to distinguish between clinically significant and nonsignificant interactions, causing some prescribers to override system alerts—and possibly miss an important warning.¹⁹ Another problem: While most systems do an excellent job of checking to see whether 2 drugs can be safely taken together, few are capable of checking for all potential interactions among multiple medications. What’s more, many drugs have not been evaluated for their potential to interact

with other agents, so the absence of reported interactions is no guarantee of a lack of DDIs.

Other strategies to consider:

■ **Minimize the number of prescriptions.** While it may not be possible to avoid prescribing a new agent for a patient who is already taking multiple medications, limiting the number of new drugs to those that are absolutely essential will help to minimize DDIs. Whenever possible, select a compound with the desired effects. Prescribe a single agent with antihypertensive as well as uricosuric effects for a patient with elevated blood pressure and uric acid levels rather than 2 different drugs (eg, losartan instead of an antihypertensive agent plus allopurinol).

■ **Alter the dosing regimen.** Several active molecules may cause DDIs by interfering with intestinal absorption or GI transit time if they’re taken closely together. For example, a quinolone should not be administered at the same time as a cation because of possible chelation in the GI tract. If a patient needs both, however, you may be able to avert a DDI by advising the patient to take them at least 2 hours apart.²⁰ Another possibility is to temporarily discontinue a maintenance

➤ **Some software programs fail to distinguish between clinically significant and nonsignificant interactions, causing some prescribers to override system alerts and possibly miss important warnings.**

Check for drug interactions: Software programs to consider

FREE

- Epocrates Rx
<http://www.epocrates.com/products/rx/>
- eRx (National ePrescribing Patient Safety Initiative)
<http://www.nationalerx.com/>

FEE-BASED

- GeneMedRx (Drug-drug and drug-gene interactions)
<http://www.genemedrx.com/provider-info.php>
 \$199/year
- iFacts (Drug Interaction Facts)
<http://www.skyscape.com/EStore/ProductDetail.aspx?ProductID=217>
 \$59.95/year
- PEPID Portable Drug Companion
<http://www.pepid.com/products/pdc/>
 \$89.95/year

medication if it has the potential to interact adversely with a drug that is needed for only a short duration.

■ Choose a different drug (or drug class).

Some drug classes should never be mixed—nitrates and phosphodiesterase type-5 inhibitors, taken together, greatly increase the risk of vasodilation and may result in severe hypotension, for example. There are also drug classes with a low potential for DDIs, including cholinesterase inhibitors and anti-hypertensives (angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, beta-blockers, and thiazides).²¹

Frequently, though, medications within the same drug class do not share the same potential for DDIs. In such cases, an adverse outcome can often be averted by being aware of combinations likely to result in clinically significant DDIs (TABLE 2) and, whenever possible, prescribing another agent. If a patient taking carbamazepine needs a macrolide antibiotic, for instance, azithromycin

is a better choice than erythromycin. That's because erythromycin inhibits the hepatic metabolism of the anticonvulsant, increasing the serum level of carbamazepine, while azithromycin does not interfere with carbamazepine metabolism.²²

How is the drug metabolized?

DDIs may occur as a result of pharmacodynamic interaction (when 2 drugs act on the same receptor, site of action, or physiologic system) or pharmacokinetic changes (interference with absorption, albumin binding, distribution, metabolism, or elimination).²³ As already noted, age-related changes in pharmacokinetics and pharmacodynamics contribute to the high prevalence of DDIs in elderly patients.

In the liver, drug metabolism, particularly via the cytochrome P450 (CYP450) system, is the cornerstone of drug transformation.²³ Although the CYP system consists of “superfamilies” with more than 100 types of enzymes, only a few are responsible for the majority of biotransformation.²³ The CYP system is also subject to genetic polymorphism, making some patients especially prone to DDIs.

P-glycoproteins (PGPs), which regulate drug absorption by transporting the drugs across cell membranes, also play a key role. PGP inhibitors or inducers help determine whether the accumulation of the molecule or the increased delivery of toxic metabolites leads to adverse effects.¹⁰

Reviewing the mechanism of action of any drug you prescribe for a patient taking other medications may alert you to a potential DDI—and the need to either switch the newly prescribed agent or alter the individual's drug regimen in some other way.

CASE ▶When John was readmitted to the hospital, he was taken off both the lovastatin and amiodarone and hydrated with forced alkaline diuresis. After a week, his symptoms resolved, and he was discharged soon after. His blood tests normalized 1 month later. The severe DDI he experienced occurred because lovastatin (which is metabolized primarily by CYP3A4) and amiodarone (a CYP3A4 inhibitor) were taken together. (Statins that are

TABLE 2

Clinically significant drug-drug interactions^{21,22}

Combination (effect)
Allopurinol and captopril (augments allopurinol's effect)
Antidepressants (SSRIs, MAOIs) and antiepileptics (augments antidepressant effect)
Clopidogrel and omeprazole or esomeprazole (reduces clopidogrel's effect)
Erythromycin and carbamazepine (augments carbamazepine's effect)
Erythromycin and terfenadine (augments terfenadine's effect)
Ketoconazole and PPIs (reduces ketoconazole's absorption)
Levodopa and metoclopramide (augments levodopa's effect)
MAOIs and narcotic analgesics (augments effects of both drugs)
Nitrates and phosphodiesterase type-5 inhibitors (augments effects of both drugs)
OCs and penicillins, phenobarbital, or tetracycline (reduces OCs' effect)
Phenobarbital and simvastatin* (reduces simvastatin's effect)
Quinolone and cation (reduces quinolone's absorption and effect)
Repaglinide and diltiazem (augments repaglinide's effect)
Simvastatin* or lovastatin and amiodarone or itraconazole (augments statin's effect)
Theophylline and cimetidine or ciprofloxacin (augments theophylline's effect)

MAOIs, monoamine oxidase inhibitors; OCs, oral contraceptives; PPIs, proton pump inhibitors; SSRIs, selective serotonin reuptake inhibitors.

*For a complete list of drugs that may interact with simvastatin, see US Food and Drug Administration.²⁸

substrates of CYP3A4 have the greatest potential for interacting with drugs known to inhibit the CYP450 system [eg, cyclosporine, morphine derivatives, ketoconazole, and amiodarone].)

This adverse interaction could have been avoided if the physician who started John on amiodarone had been aware of the potential DDI—and switched him to an HMG-CoA inhibitor other than lovastatin. Pravastatin, which is *not* metabolized via CYP450, would have been an excellent choice.

Warfarin warrants special attention

Medications that have a particularly high potential for adverse interactions require special attention and patient monitoring, warfarin foremost among them. Warfarin metabolism and its anticoagulant effects can be dramatically changed if it is administered with a drug with a higher affinity for PGPs or an agent that competes with it within the

CYP450 system.²⁴ Because of warfarin's narrow therapeutic range, there are many drugs and drug classes that patients on warfarin should avoid (TABLE 3)—a fact that patients as well as their physicians need to be aware of.²⁴ Indeed, warfarin is often involved in drug-related hospital admissions for DDIs, especially in elderly patients and in those who are also taking nonsteroidal anti-inflammatory drugs (NSAIDs) or macrolides—2 of the many drug classes that patients taking warfarin should avoid.²⁴

Keep an eye on these drug combinations, as well

Among the many combinations likely to result in clinically significant DDIs (TABLE 2), the following are worth mentioning:

■ **Clopidogrel + certain proton pump inhibitors.** The addition of a PPI to clopidogrel

>
Clinically significant interactions can often be averted by prescribing a different agent within the same drug class.

TABLE 3

Patient on warfarin? Steer clear of these drugs^{10,20,23}

Drug class: agent(s)
Antiarrhythmics: amiodarone, propafenone
Antibiotics: ciprofloxacin, metronidazole, rifampin, trimethoprim/sulfamethoxazole
Anticonvulsants: carbamazepine, valproate
Antidepressants: fluoxetine, fluvoxamine, paroxetine, sertraline, trazodone
Antidiabetics: chlorpropamide
Antifungals: danazol, fluconazole, itraconazole, miconazole
Antimalarial agents: quinidine
Antineoplastics: azathioprine, fluorouracil, flutamide, ifosfamide, tamoxifen
Antiplatelet agents: ticlopidine
Antipsychotics: clozapine
Diuretics: spironolactone
GI drugs: cimetidine, esomeprazole, lansoprazole, omeprazole, pantoprazole, rabeprazole, ranitidine
Gout treatment: allopurinol
Hypolipidemics: atorvastatin, cholestyramine, ezetimibe, fenofibrate, fluvastatin, gemfibrozil, lovastatin, pravastatin, simvastatin
NSAIDs: aspirin, celecoxib, diclofenac, ibuprofen, indomethacin, ketoprofen, ketorolac, naproxen, piroxicam, sulindac
Thrombolytics: heparin, tissue plasminogen activator
Thyroid drugs: methimazole, propylthiouracil
Uricosuric agents: sulfinpyrazone

GI, gastrointestinal; NSAIDs, nonsteroidal anti-inflammatory drugs.

➤ Warfarin is often involved in hospital admissions for drug-drug interactions—especially in elderly patients and those who are also taking NSAIDs or macrolides.

has been associated with a significant increase of recurrent infarction.²⁵ This may occur because clopidogrel is a prodrug and is converted in the liver to its active form by CYP2C19, an enzyme specifically inhibited by various PPIs—thereby altering the effectiveness of the antiplatelet agent. However, a recent analysis suggests that there is no need to avoid the concomitant use of a PPI and clopidogrel—and that the interference appears to be limited to omeprazole and esomeprazole.²⁶

■ **Oral contraceptives (OCs) + penicillins, phenobarbital, or tetracycline.** Each of these drugs reduces the effect of OCs, and women who are taking them concomitantly need to be advised to use another means of contraception.

■ **Phenobarbital + simvastatin.** Pheno-

barbital (a CYP3A4 inducer) may reduce the efficacy of simvastatin.

■ **Repaglinide + diltiazem.** Diltiazem inhibits the metabolism of repaglinide (a CYP3A4 substrate), thus increasing the risk of hypoglycemia.

■ **Simvastatin + amiodarone or itraconazole.** Either of these antiarrhythmic agents decreases simvastatin metabolism, raising the risk of myopathy; with amiodarone, however, the likelihood of an adverse outcome is especially high. In 2008, the US Food and Drug Administration (FDA) issued a warning to healthcare professionals of the increased risk for rhabdomyolysis when simvastatin doses greater than 20 mg are administered together with amiodarone.²⁷ The agency issued a safety review of simvastatin, warning of its

potential for DDIs with amiodarone and numerous other medications, earlier this year.²⁸

As John's case illustrates, use of lovastatin with amiodarone should be avoided, as well.

Keep others safe: Report adverse events

When a DDI occurs despite your best efforts, you can help ensure that other patients do not experience the same adverse outcome by re-

porting it to MedWatch, the FDA's voluntary safety information and adverse event reporting program. Go to <https://www.accessdata.fda.gov/scripts/medwatch/medwatch-online.htm> to file a report online. **JFP**

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Be sure to report adverse drug-drug interactions to MedWatch at: <https://www.accessdata.fda.gov/scripts/medwatch/medwatch-online.htm>.



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