

# Dangerous and Deadly Drug Combinations

## Drug Interaction Checker

<http://reference.medscape.com/drug-interactionchecker>

### Drug/Drug Interactions

In the polypharmacy era, it is not unusual for patients with chronic disease to be taking a half-dozen or more different drugs. Drug interactions have increased because we are using more drugs, and more combinations of drugs, than ever before. Drug/drug interactions can impair the effectiveness of one or more drugs, or result in other adverse events.

Drug/drug interactions are considered preventable errors. With the advent of electronic prescribing, the hope was that software would warn prescribers about interactions between one or more drugs that the patient is taking, and these alerts are common. They are so ubiquitous, in fact, that alerts are often overridden in the prescribing process. Clinicians cannot rely on prescribing software to prevent all drug-drug interactions.

Douglas S. Paauw, MD, professor of medicine at the University of Washington School of Medicine in Seattle, provides examples of common drug/drug interactions and methods of prevention. The following examples are not ranked in any order of frequency or clinical significance.

### St John's Wort and Potentially Lifesaving Drugs

The popularity of botanical dietary supplements in recent decades has led to increased recognition of potentially dangerous interactions between some herbal products and conventional drugs. In some cases, as with St John's wort (*Hypericum perforatum*), the danger lies in an interaction that can reduce the efficacy of a conventional drug that may be critical to the patient's health.

Documented interactions between St John's wort and conventional drugs include reduced blood cyclosporine concentrations resulting in transplant rejection, serotonin syndrome when taken concurrently with serotonin reuptake inhibitors, unwanted pregnancies in women taking oral contraceptives, reduced plasma concentrations of antiretroviral drugs (indinavir, nevirapine) and a possible increase in resistance to these drugs, and reduced effectiveness of anticancer agents (irinotecan, imatinib). Hyperforin is believed to be the bioactive component of St John's wort responsible for not only its antidepressant action but also its interactive effects. Hyperforin induces CYP3A4/CYP3A5, causing the medications listed above—some of which are potentially lifesaving—to be metabolized more quickly, leading to low blood levels and less effectiveness.

It is therefore critical for clinicians in every area of practice, regardless of medical specialty, to ask patients about their use of herbal supplements, such as St John's wort.

### Serotonin Syndrome

Selective serotonin reuptake inhibitors (SSRIs) are widely prescribed drugs. Serotonin syndrome is a potentially life-threatening syndrome precipitated by the use of serotonergic drugs that cause over activation of both the peripheral and central postsynaptic 5HT-1A and 5HT-2A receptors. Features of serotonin syndrome include mental status changes, neuromuscular hyperactivity, and autonomic hyperactivity. One cause of serotonin syndrome is an interaction between two serotonergic drugs that work by different mechanisms, such as a SSRI or a serotonin/norepinephrine reuptake inhibitor (SNRI) coadministered with tramadol, trazodone, dextromethorphan, or linezolid. The higher the dose of SSRI, the more likely that a drug interaction will occur.

Clinicians are often concerned about the theoretical risk for serotonin syndrome when prescribing a triptan for prevention of migraine in a patient who is taking a SSRI or a SNRI. An alert often pops up during electronic prescribing when this combination of drugs is selected. Although caution and vigilance are

warranted, the evidence does not support avoiding the use of triptans in these patients, unless they are taking other serotonergic drugs in addition to the SSRI.

## **Statins Plus CYP3A4 Inhibitors**

Statins (3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors) are widely prescribed, and widely recognized to carry a high risk for drug/drug interactions. Owing to differences in elimination pathways, however, not all statins pose the same risk. The most likely statins to interact with another drug are simvastatin and lovastatin; less likely are pravastatin and rosuvastatin.

Although rhabdomyolysis can occur on high-dose statin monotherapy, the risk for this condition is increased with concomitant use of certain drugs. Potent inhibitors of cytochrome P450 3A4 (CYP3A4) can significantly increase the serum concentrations of the active forms of simvastatin, lovastatin, and atorvastatin. The drugs most likely to interact with statins include the fibrates (especially gemfibrozil), azole antifungal agents, amiodarone, macrolides (especially erythromycin and clarithromycin, but not azithromycin), protease inhibitors (eg, ritonavir), and calcium-channel blockers (especially verapamil and diltiazem).

The use of non-CYP3A4-metabolized statins (eg, pitavastatin) is preferred for patients taking other drugs that inhibit the CYP3A4 pathway. If prescribing a drug with a potential interaction with a statin is unavoidable, nonconcurrent dosing can minimize the risk for interactions. Giving the drug doses 12 hours apart, if possible, will prevent drug levels of the two agents from peaking at the same time.

## **Clarithromycin and Calcium-Channel Blockers**

Coadministration of clarithromycin with vasodilating calcium-channel blockers, such as amlodipine and felodipine, can cause hypotension and acute renal failure. Clarithromycin impairs the action of nifedipine by inhibiting CYP3A4 metabolism, resulting in hypotension—a serious but underappreciated risk. Other macrolides may also precipitate this interaction when given concomitantly with calcium-channel blockers, including erythromycin. Azithromycin, which does not inhibit CYP3A4, is the preferred agent when a macrolide is necessary in a patient taking a calcium-channel blocker.

Other potentially serious drug interactions can occur when clarithromycin is taken with statins (especially, for example, simvastatin or lovastatin) and colchicine. Taking clarithromycin with glipizide or glyburide can result in hypoglycemia. In fact, 82 major drug interactions have been reported with clarithromycin.

## **TMP/SMX and Antihypertensive Agents**

Trimethoprim/sulfamethoxazole (TMP/SMX) is an important potential cause of hyperkalemia in elderly patients and those with chronic kidney disease, especially with concomitant use of angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs).

With the emergence of community-acquired methicillin-resistant *Staphylococcus aureus*, and escalating fear about this pathogen, prescriptions for TMP/SMX are on the rise. The trimethoprim component acts like amiloride (a potassium-sparing diuretic) and can increase serum potassium to life-threatening levels. Sudden death has been reported in patients taking TMP/SMX who also take an ACEI or ARB. The risk seems to be limited to TMP/SMX. In a population-based study, no other antibiotic given concurrently with an ACEI or ARB was associated with hyperkalemia.

## **Warfarin and Acetaminophen**

Patients on warfarin are often advised to choose acetaminophen for analgesia because nonsteroidal anti-inflammatory drugs (NSAIDs) can increase the risk for gastrointestinal bleeding. The interaction between warfarin and acetaminophen has been a well-kept secret. Many prescribers are unaware of the substantial data showing that regular use of acetaminophen increases the international normalized ratio (INR). Patients on warfarin should be monitored closely, and an INR should be obtained 3-5 days after patients begin taking daily acetaminophen. This is not necessary for an occasional dose of acetaminophen. Therefore, when a patient on warfarin experiences an unexplained jump in INR, it is worth asking about the use of acetaminophen.

Also, prednisone often raises the INR and can be an overlooked cause of an INR increase in patients on warfarin therapy. Maintaining awareness that the INR might increase transiently during a short course of prednisone can avoid an unnecessary adjustment of the patient's warfarin dose. A mild increase in INR can be tolerated for a short time, but clinicians should be cautious, especially if the patient is taking another drug that increases INR (eg, TMP/SMX).

## **Antihypertensive Drugs and NSAIDs**

NSAIDs are among the most widely used medications, and have often been associated with elevated blood pressure. NSAIDs block both cyclooxygenase (COX)-1 and COX-2 enzymes, which impairs prostaglandin synthesis. Prostaglandin inhibition, in turn, increases arterial smooth-muscle tone and produces a dose-related effect on natriuresis, resulting in fluid retention. By these mechanisms, NSAIDs can reduce the effectiveness of some of the most commonly used antihypertensive agents (diuretics, ACEIs, and ARBs). Because NSAIDs are available without a prescription, patients may be aggravating their hypertension by using these drugs. The NSAIDs with the most profound effect on blood pressure are indomethacin, piroxicam, and naproxen. NSAIDs that have an intermediate effect on blood pressure include ibuprofen, rofecoxib, and celecoxib, although the magnitude of this effect is still under investigation. Aspirin does not significantly increase blood pressure, even in patients with hypertension.

In addition to blunting the hypotensive effects of diuretics, ACEIs and ARBs can increase the risk for acute renal failure when an NSAID is coadministered. The so-called "triple therapy" (ACEI or ARB, a diuretic, and an NSAID) has been shown to increase the risk for acute kidney failure by 31%. Clinicians and pharmacists should ask patients being treated for hypertension about their use of NSAIDs, especially those whose hypertension is not responding to other treatments.

## **Thyroid Hormone and Proton Pump Inhibitors**

Thyroid supplementation is extremely common. Some frequently used drugs, including proton pump inhibitors (PPIs), statins, iron, calcium, magnesium, raloxifene, and estrogens, can interfere with thyroid hormone absorption, causing patients whose disease was previously well-controlled on a thyroid hormone to develop hypothyroidism. Estrogen has a binding effect and requires an increased dose of thyroid hormone.

The interaction between levothyroxine and omeprazole in patients with impaired gastric acid secretion requires an increased dose of oral thyroxine, which suggests that normal acid secretion is necessary for effective oral absorption of thyroxine. Patients with hypothyroidism who are euthyroid and on levothyroxine may need thyroid function testing after initiation of a PPI, especially if symptoms of hypothyroidism emerge. And those with impaired gastric acid secretion may require an increased dose of levothyroxine to keep the thyroid-stimulating hormone level within range.

The product labeling for levothyroxine recommends that it not be administered simultaneously with antacids because of the binding effect of calcium or magnesium in the antacid. If concurrent use is necessary, administration of the agents should be separated by 4 hours.

## **Grapefruit Juice and Drug Interactions**

A review of important drug interactions would not be complete without mentioning grapefruit juice, which can increase drug levels by interfering with drug metabolism, primarily mediated by chemicals in the juice that inhibit the CYP3A4 drug-metabolizing enzyme in the small intestine. This inhibition reduces the first-pass metabolism of drugs using the CYP3A4 intestinal system, thereby increasing the bioavailability and maximal plasma drug concentrations of the CYP3A4 substrates. The effect of grapefruit juice on drug metabolism is most pronounced in drugs with a high first-pass metabolism (eg, felodipine, amiodarone). Other important drugs affected by grapefruit juice are some of the statins (simvastatin and lovastatin, and atorvastatin to some degree, but not pravastatin), cyclosporine, amlodipine, and nifedipine.

Patients have heard about this interaction and worry about it. It is probably a more significant issue in the presence of other drug interactions (eg, simvastatin, verapamil, and grapefruit juice).

*Source: Medscape.com*