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AHC Media

Dangerous Drug Interactions

My emergency department (ED) has had an electronic medical record for the past two years. Part of that record includes a medication list that is created from past encounters and updated by the triage nurse. Because it is electronic and prints out nicely in the triage summary, it has the appearance of truth. My experience with the list is likely similar to some of yours: Patients are often taking medications not on the list and are not currently taking those that are. So, my caution to the residents before prescribing any new medication is to ask patients if they are currently taking any of the medications on the list or taking anything not listed. That way, we can minimize the potential for some for the dangerous drug interactions discussed in this review.

— J. Stephan Stapczynski, MD. Editor

Background

Drug interactions have become more common because of the increased use of multiple prescription drugs, advancing age of the population, and the complexities of modern health care. For example, the average American adult who is 55 years old or older uses 6 to 9 medications daily.[1] The high-profile deaths of artists and celebrities due to the use of medications and drugs have brought incredible attention to this subject by both the media and the public. In addition, a 1999 Institute of Medicine report highlighted drug reactions (including interactions) as one of the reasons for preventable mortality in the United States.

Interactions are defined as situations in which a substance affects the activity of a drug. The drug's effects can be either increased or decreased, or a new effect can be produced that neither the substance nor drug previously exhibited.[2] Although most drug interactions are between two or more drugs, other important drug interactions can involve drugs with herbs as well as drugs with foods.[2]

In general, drug interactions must be avoided because the effect can have an unexpected, unpredictable, or adverse outcome. However, certain drug interactions are produced intentionally because they can be clinically beneficial. These clinically useful interactions are known as pharmacologic augmentations or pharmacologic synergisms. One historic example of pharmacologic augmentation was the use of probenecid with penicillin. Initially, penicillin was very difficult to manufacture. Probenecid was added to penicillin, as it helped delay the renal excretion of penicillin, thereby prolonging its clinical effect.[2] A modern example is the use of carbidopa with levodopa in the management of Parkinson's disease. Levodopa, when used individually, is metabolized in the peripheral tissues. This decreases the availability of levodopa in the brain and increases the risk of adverse effects. Carbidopa inhibits the peripheral metabolism of levodopa, allowing more unmetabolized levodopa to reach the brain, therefore increasing clinical efficacy and reducing the risk of peripheral side effects.

Epidemiology

Drug interactions are a leading cause of morbidity and mortality in the

Executive Summary

- Polypharmacy and drug interactions are common in patients older than 55 years.
- Review a patient's medication list before initiating or prescribing a new drug in the ED.
- Be extra cautious when initiating a new drug in a patient taking chronic warfarin therapy.
- Know that some drugs commonly used in the ED (e.g., haloperidol) have "Black Box" warnings from the FDA regarding QT interval prolongation.

United States because the rates of per-capita prescription medication use have considerably increased in the past few decades, as have the rates of use of over-the-counter medications and supplements.[3] In a medication survey of residents of a senior community, 4% of those older than 55 years of age are taking a medicine that puts them at risk for a drug interaction, with about half of those involving non-prescription drugs (over-the-counter medications, supplements, or herbs).[1] Because of the common use of prescription, over-the-counter drugs and herbals, drug errors and adverse drug effects are the most common cause of iatrogenic illness in the United States.[4]

Drug interactions frequently occur in high acuity areas of the hospital, such as the intensive care unit (ICU) and the ED. In a recent study of more than 400 ICU patients, 225 patients had a potential drug interaction. The most commonly reported drug interactions included anticoagulation problems, QT prolongation, and p450 inhibition. Of the reported drug interactions in the study, 5-9% were considered major or contraindicated drug combinations.[5] In the ED, a study found that patients are at a high risk for a drug interaction if they are younger than 50 years of age and taking more than three medications daily or if they are older than 50 years of age and taking more than two daily medicines.[6]

Drug interactions result in excess hospitalizations. In one study, drug-drug interactions were responsible for 0.57% of hospitalizations, but this number rose to 4.8% in the elderly.[7] The drugs most commonly involved in this study were nonsteroidal anti-inflammatory drugs (NSAIDs) and cardiovascular drugs. The most common reasons for admission due to these drug interactions were gastrointestinal bleeding (GI) bleeding, hypertension, hypotension, and cardiac rhythm disturbances.[7]

Patients in the hospital can also be discharged with multiple drugs that can cause significant interactions. A review of hospitalized patients' medication profiles upon hospital discharge showed that 62.5% of patients had been discharged with a potential drug interaction. Of these, 38% were of moderate severity, and 2% were considered of major severity.[8]

Unintentional poisoning caused 20,000 deaths in 2004, making it the second leading cause of accidental death in the United States.[9] Therefore, it is of no surprise that drug-related morbidity and mortality have been estimated to cost more than $130 billion per year in the United States alone.[4]

Demographics

The elderly are at risk for developing drug interactions due to their overall increased risk of developing illness and, therefore, increasing their use of prescription and over-the-counter medications. As mentioned previously, the elderly are more likely to take multiple medications. Although individuals older than 65 years of age represent only 13% of the total U.S. population, it has been estimated that they consume nearly one-third of all medications in the United States.[10] This increased use of medications in the elderly, combined with their decreased metabolism and impaired clearance of medications, greatly increases their risk for developing drug interactions.[11-13]

Critically ill patients are also at risk for developing drug interactions due to the fact that they are exposed to a large number of drugs during their illness. In addition, critically ill patients are likely to have organ dysfunction resulting in impaired metabolism and clearance of drugs. In one ICU study from Europe published in 1997, 70 patients were evaluated for possible drug interactions. More than 100 drug interactions were found among 44.3% of those patients (an average of 1.5 interactions per patient). On average, these ICU patients were receiving more than 14 drugs per patient, with digoxin causing the most interactions.[14]

Other populations at risk for developing drug interactions include psychiatric patients; patients taking high doses or multiple medications due to resistant medical conditions; poly-drug misusers and abusers; and patients in undeveloped countries who self-medicate with prescription medications easily obtained over-the-counter.[11] Patients who have low albumin levels from chronic lung disease, alcoholism, or malnourishment are also at risk of developing significant drug interactions due to altered protein binding.[15]

Pathophysiology — Mechanisms of Drug Interactions

Drug interactions can occur at any stage during or after drug administration, and even prior to administration. In general, following administration, there are two major types of interactions: pharmacokinetic interactions (how the body interacts with a drug, usually related to absorption, distribution,

Table 1: Mechanisms of Drug Interactions

Interaction Type	Examples of Drug Interactions
Prior to IV administration	• Diazepam: Poor solubility • Precipitation of catecholamines with sodium bicarbonate
Prior to intestinal absorption	• Anticholinergics: slowed absorption • Antacids, histamine 2 blockers, and PPIs: Changes in pH can affect drug absorption (itraconazole, ketoconazole, and cefpodoxime)[4] • Broad spectrum antibiotics: Eliminate vitamin K-producing bacteria in the gut (warfarin reaction)[2] • Cholesterol resins (cholestyramine): Can bind other drugs and decrease their absorption (warfarin, digoxin, thyroid hormone, beta-blockers, thiazides, fibric acid drugs)[4] • Metoclopramide: Hastens absorption
During intestinal absorption	• "First pass metabolism" and cytochrome 450 enzyme alterations
Protein binding	• Displacement from albumin and other proteins: • Warfarin and sulfonamide antibiotics[2] • Diazepam displaces phenytoin from plasma proteins[2,11]
Interactions at site of metabolism	• Due to p450 alterations; takes 4-6 weeks for peak effects[18] • When induced, drug metabolism is exaggerated; when inhibited, drug metabolism is delayed[19]
Interactions at site of secretion (renal)	• Probenecid decreases penicillin excretion • Salicylates and NSAIDs decrease methotrexate excretion • Cimetidine decreases metformin elimination • Indomethacin inhibits renal prostaglandins. This reduces renal blood flow and decreases drug elimination. • Changes in urine pH: Aspirin's excretion is enhanced by urine alkalinization[2]
Pharmacodynamic interactions	• Antagonism: Drugs with opposing pharmacologic actions diminish the physiologic response • Agonism (synergism): Drugs with similar effects increase the physiologic response

metabolism, and elimination); and pharmacodynamic interactions (how the drug interacts with the body, usually related to receptor-mediated physiological effects). Table 1 summarizes some of these interactions.[2]

Drug metabolism is defined as the biochemical modification of drugs by enzymatic processes. Its purpose is to convert drugs to a more water-soluble form so they can then be renally excreted. Drug metabolism is divided into two phases:

• Phase 1 (also known as non-synthetic reactions) involves several different reactions, including oxidation, reduction, hydrolysis, cyclization and decyclization, addition of oxygen, or removal of hydrogen from a drug. This phase usually is achieved in the liver utilizing the cytochrome P450 (CYP450) enzymes.

• Phase 2 metabolism (also known as the conjugation reactions) involves several mechanisms, including methylation, sulfation, acetylation, and glucuronidation. These reactions make the Phase 2 metabolized drug more water-soluble and usually also inactivate the drug.

The CYP450 enzymes are the major enzymes that play a vital role in the metabolism of drugs. Greater than 75% of a drug's metabolism is accomplished by the CYP450 enzymes.[16] The resultant metabolites can be the active form of a drug, an inactive form, or substances that can be more or less potent than the parent compound.[11] Many drugs and other substances, including foods and herbs, can increase (induce) or decrease (inhibit) the activity of CYP450. These changes in enzyme activity result in drug interactions due to altered metabolism and clearance of many drugs.[16]

There are many CYP450 isoenzymes, but a few are very relevant in clinical practice: CYP3A4 is induced by many drugs, such as carbamazepine, phenytoin, phenobarbital, rifampicin, and St. John's wort. This induction will augment drug metabolism and, therefore, decrease another drug's efficacy.[11,17] However, CYP450 inhibition (or two drugs competing for the same isoenzyme), leading to increased drug levels, is probably most important in drug toxicity and interactions.[11] For example, CYP2C9 is involved in the metabolism of warfarin. Alterations in the activity of this enzyme can result in increased anticoagulation.

Relevant Drug Interactions for the ED Physician

Warfarin Interactions. Drug

Table 2: Selected Drug Interactions with Warfarin

Increased Effect of Warfarin (Elevated INR)	Decreased Effect of Warfarin (Low INR)
Amiodarone	Barbiturates
Azole antifungals (fluconazole)	Carbamazepine
Cephalosporins	Cholestyramine
Cimetidine	Cigarette smoking
Ethanol	Corticosteroids
Fluvastatin	Oral contraceptives
HMG-CoA reductase inhibitors (Lovastatin)	Phenytoin
Isoniazid	Primidone
Macrolides (clarithromycin, erythromycin)	Rifampin
Metronidazole	St. John's wort
NSAIDs, acetaminophen, aspirin	Vitamin K
Quinolones (ciprofloxacin)	
Tricyclic antidepressants	

interactions with warfarin are common and they place the patient at risk for major bleeding or thrombotic complications.

Drug interactions with warfarin can be either pharmacokinetic or pharmacodynamic in nature. Pharmacokinetic drug interactions are usually related to the metabolism of warfarin. Warfarin contains the isomers R and S. The S isomer is more potent and is metabolized by CYP 2C9, while the less potent R isomer is metabolized by CYP 1A2 and 3A4.[20] Drugs that inhibit CYP 2C9, such as trimethoprim/sulfamethoxazole, can be expected to have a significant effect on the international normalized ratio (INR).[21] Avoid these medications in patients taking warfarin or closely monitor the INR.[4] (*See Table 2.*) Drugs have less impact on the R isomer due to its metabolism with multiple enzymes and decreased biological activity.[22,23] Drugs that induce CYP450 enzymes, especially 2C9, can reduce the effect of warfarin and necessitate higher warfarin doses during treatment. Rifampin is the most common offender.[4,22]

Pharmacodynamic interactions with warfarin can also influence the safety and efficacy of anticoagulation therapy. These interactions are not as numerous as the pharmacokinetic interactions. The most common interaction with warfarin is the concomitant use of antiplatelet agents such as prescription and non-prescription NSAIDs and clopidogrel. These agents can increase bleeding risk and severity without affecting the INR. The platelet dysfunction caused by aspirin increases the risk of severe bleeding.[24] Aspirin with warfarin was found to increase the risk of bleeding compared to warfarin alone by doubling the risk of intracranial hemorrhage (~1.5% per year).[25] Certain herbals, such as garlic and dong quai, may also have antiplatelet effects, but these interactions are less predictable and the evidence for them is not well established.

Other forms of pharmacodynamic interactions can also affect the INR. Levothyroxine increases the catabolism of clotting factors, and vitamin K-containing foods (i.e., green leafy vegetables) increase the production of clotting factors, thereby causing INR depression.[26] Even acetaminophen has been associated with higher INRs in patients taking warfarin when doses greater than 1.5 grams per day are used.[27]

Angiotensin-Converting Enzyme (ACE) Inhibitor Interactions. ACE inhibitors decrease the production of aldosterone, resulting in decreased potassium excretion in the distal nephron. Significant hyperkalemia usually does not occur in patients with normal renal function who are not taking other medications that cause potassium retention. However, life-threatening hyperkalemia may result in patients taking ACE inhibitor therapy when potassium homeostasis is disturbed by increased potassium intake, decreased potassium excretion, or abnormal cellular uptake. Severe cases usually involve elderly patients with precipitating factors of dehydration, renal insufficiency, and heart failure.

Notable drug interactions with ACE inhibitors that result in hyperkalemia due to decreased potassium excretion include potassium-sparing diuretics (such as amiloride, spironolactone, and triamterene), NSAIDs, trimethoprim, and cyclosporine.[4] Hyperkalemia due to increased potassium intake may occur with potassium supplements or penicillin G potassium, while hyperkalemia due to abnormal cellular uptake and distribution of potassium may result from interactions with beta-adrenergic blockers, digoxin, or succinylcholine.

Digoxin Interactions. Digoxin has a narrow therapeutic index and is excreted by the kidneys, allowing several drug interactions and clinical conditions to easily alter the clinical efficacy of digoxin or result in toxicity. Dehydration, renal insufficiency, electrolyte abnormalities, acid-base disturbances, and congestive heart failure all increase the susceptibility to toxicity from digoxin-related drug interactions. Table 3 summarizes the most important drug interactions with digoxin.

Interactions that Result in QT Interval Prolongation. Many different medications cause prolongation of the QT interval of the electrocardiogram, increasing the risk of ventricular arrhythmias, especially torsades de pointes (TDP) and sudden cardiac death.[28,29] The risk of such adverse effects is dramatically increased when QT interval-prolonging medications are taken in combination, especially if the patient has underlying conditions such as bradycardia or hypokalemia

Table 3: Selected Drug Interactions with Digoxin

Effect	Drugs
Increased serum levels	Amiodarone Benzodiazepines Cyclosporine Itraconazole Indomethacin Macrolides Omeprazole Propafenone Quinidine Tetracyclines Verapamil
Decreased serum levels	Albuterol Aminoglycosides (oral) Aluminum/magnesium antacids Activated charcoal Cholestyramine Rifampin St. John's wort Sulfasalazine
Enhanced pharmacodynamic effects	Beta-blockers Calcium channel blockers Cyclosporine Diuretics Sympathomimetics
Antagonize pharmacodynamic effects	Thyroid hormone

that also predispose to development of TDP. Historically, a number of drugs have been withdrawn from the U.S. market due to these concerns, including astemizole, cisapride, and terfenadine.[4,29] Notable classes of medications that prolong the QT interval include certain antiarrhythmics, antidepressants, antihistamines, antimicrobials, antipsychotics, azole antifungals, and protease inhibitors.[18,28-34] (*See Table 4.*)

Serotonin Augmentation. Serotonin syndrome, or serotonin hyperactivity syndrome, usually results when two or more serotonergic medications are combined, although it may occur with therapeutic doses or overdoses of a single serotonergic agent. It is thought to be mediated by excessive stimulation of serotonin 5-HT2A and 5-HT1A receptors.

The syndrome has a spectrum of severity from mild serotonin excess to life-threatening toxicity. The clinical diagnostic criteria include autonomic excitation (tachycardia, hypertension, diarrhea, diaphoresis), altered mental status, and increased muscle tone (myoclonus, tremor, hyperreflexia).[35] There are no laboratory tests that can be used to confirm the diagnosis of serotonin syndrome.

A large number of drugs and drug interactions have been associated with serotonin syndrome, as many drugs alter serotonin transmission as a minor or major pharmacologic action.[31] Increased serotonergic activity may be caused by a number of mechanisms, including direct serotonin agonism, increased synthesis, increased release, decreased breakdown, inhibition of re-uptake, and increased serotonergic tone.[35] Table 5 summarizes drugs associated with serotonin excess.

Miscellaneous Interactions

Phosphodiesterase 5 (PDE5) inhibitors,[37,38] such as sildenafil, tadalafil, and vardenafil, are prescribed to treat erectile dysfunction and pulmonary hypertension and are well known to interact with organic nitrates, producing significant hypotension.[41] This is an example of a pharmacodynamic drug interaction, as the hypotension is due to a similar mechanism of action of the two medications. Nitrates increase the production of cyclic guanosine monophosphate (cGMP), resulting in vascular smooth muscle relaxation, while PDE5 inhibitors inhibit the breakdown of cGMP by the enzyme phosphodiesterase. This is a potentially common drug interaction because there is significant overlap in the risk factors for erectile dysfunction and the risk factors for which a patient may receive nitrates, such as angina and congestive heart failure.

Current American College of Cardiology and American Heart Association recommendations are to avoid administration of nitrates to patients who have used tadalafil in the past 48 hours due to its longer half-life, and in the past 24 hours for the other PDE5 inhibitors. Similarly, PDE5 inhibitors should be avoided in patients who are treated chronically with nitrates.[42]

Some patients develop orthostatic hypotension when a PDE5 inhibitor is used in conjunction with an alpha-blocking agent such as doxazosin, tamsulosin, and terazosin (typically for hypertension or benign prostatic hypertrophy). Some studies suggest that this drug interaction is less significant if the patient has been on long-term alpha-blocker therapy.[42] Hypotension, however, does not typically occur with the concomitant use of other classes of antihypertensive drugs (ACE inhibitors, angiotensin receptor blockers, beta-blockers, calcium channel blockers, and diuretics).[42]

Sildenafil is metabolized by CYP3A4, and, therefore, its adverse effects may be increased in patients who are prescribed other

Table 4: Drugs that Prolong the QT Interval

Drug Family	Drug Family
Antiarrhythmics 1A: disopyramide, procainamide, quinidine 1C: flecainide, encainide III: amiodarone, ibutilide, sotalol	Azole antifungals (ketoconazole, miconazole, itraconazole)
Antidepressants (tricyclics, SSRIs, lithium)	Calcium channel blockers (diltiazem, verapamil)
Antihistamines (astemizole, diphenhydramine, hydroxyzine, terfenadine)	Protease inhibitors
Antimicrobials (amantadine, quinine, chloroquine, ciprofloxacin, macrolides, pentamidine)	Others: Arsenic Cisapride Methadone Organophosphates Vasopressin
Antipsychotics (chlorpromazine, droperidol, haloperidol, ziprasidone)	

medications that are metabolized by this enzyme. Such medications include macrolide and imidazole antibiotics, HMG-CoA reductase inhibitors, and highly active antiretroviral therapy (HAART).[43] Sildenafil also may cause a prolonged QT interval by blocking the rectifying K current and therefore delaying repolarization.[44]

Proton Pump Inhibitors (PPIs) and Clopidogrel.[41] The use of clopidogrel combined with a PPI has been the subject of recent controversy with the concern for a drug reaction resulting in decreased efficacy of clopidogrel and the potential for worsened cardiovascular outcomes.[45] This has resulted in product labeling changes and advisories from organizations including the U.S. Food and Drug Administration (FDA).

A consensus document was published in 2010 by an expert panel from the American College of Cardiology, the American Heart Association, and the American College of Gastroenterology that reviewed the literature on this drug interaction.[46] The panel concluded that, although there is a potential interaction between omeprazole and clopidogrel that could decrease the efficacy of clopidogrel, this does not seem to translate to cardiovascular harm. The studies that suggested cardiovascular harm were all observational and retrospective studies. The only prospective trial, the COGENT trial, showed no demonstrable cardiovascular harm. In fact, it showed a demonstrable gastrointestinal (GI) protective benefit in the patients who were prescribed the combination of omeprazole plus clopidogrel.[47] Patients taking clopidogrel therapy who are at low risk for GI complications may be prescribed H2 blockers instead of a PPI. However, patients at moderate to high GI risk can still be treated with a PPI.

Aspirin (ASA) and Ibuprofen. This interaction is important for those with coronary artery disease (CAD) who benefit from the full antiplatelet effect of the salicylates.[45] It has been demonstrated that ibuprofen interferes with the antiplatelet activity of low-dose ASA when they are ingested concurrently. The mechanism by which this occurs may be through competitive inhibition of the acetylation site of cyclooxygenase (COX) in the platelet. Both ibuprofen (reversible inhibition) and ASA (irreversible inhibition) occupy nearby sites on COX, such that the presence of ibuprofen interferes with ASA binding. Once the ibuprofen releases from the binding site, COX will not be fully inhibited because some ASA will already have been excreted. The net effect is a decrease in the aspirin-mediated irreversible inhibition of thromboxane B2 (TXB2) production and, therefore, less inhibition of platelet aggregation.[45]

The clinical implication of the interference by ibuprofen on the anti-platelet effect of ASA is unclear. Acetaminophen does not appear to interfere with the antiplatelet effect of low-dose ASA. Therefore, it is safer to use acetaminophen or narcotic analgesics in patients who need the full protection of ASA. Otherwise, space the dosing between the NSAIDs and ASA by 8 hours.[45]

Food Drug Interactions

Interactions between foods and drugs can have a profound influence on the efficacy of drug therapy and adverse drug effects. Such interactions are common, and can range from minor to harmful or even fatal. It is challenging for the clinician to identify food-drug interactions because food consumption is not usually documented in the medical record. In addition, new drugs are reaching the market with ever-increasing speed, and less information is available about their adverse effects and interactions at the time of release. These difficulties are also compounded by genetic differences that determine the susceptibility of individual patients. Some of the more important food-drug interactions are discussed below.

Monoamine oxidase (MAO) is a mitochondrial enzyme that is found in nerve terminals, the liver, intestinal mucosa, and other organs. It regulates the metabolic degradation of catecholamines and serotonin in the CNS or peripheral tissues, and, therefore, monoamine oxidase inhibitors (MAOI) have been used therapeutically to treat depression and Parkinson's disease. However,

Table 5: Selected Drugs that Increase Serotonergic Activity

Antidepressants (trazodone, venlafaxine, mirtazapine)	MAOIs (phenelzine, moclobemide, clorgyline, isocarboxazid)[36]
Cocaine, amphetamines[37]	Meperidine[38]
Dextromethorphan[39]	St. John's wort (hyperforin)[36]
L-tryptophan	SSRIs (fluoxetine, citalopram, paroxetine, fluvoxamine, sertraline)
Linezolid (weak MAOI)[37]	Pentazocine[38]
Lithium	Triptans[39]
LSD	Tramadol[40]

this mechanism of action has resulted in several important drug-drug and food-drug interactions with MAOI.

An important food-drug interaction occurs when an MAOI is combined with foods or beverages containing the amino acid tyramine, an indirectly acting sympathomimetic agent. When the metabolism of tyramine is inhibited by an MAOI, a significant release of norepinephrine occurs, resulting in marked hypertension, hyperthermia, cardiac arrhythmias, and cerebral hemorrhage. Tyramine is found in a number of foods, including chocolate and a variety of aged, fermented, overripe, pickled, or yeast-containing foods and beverages such as beer, wine, cheeses, avocados, and some processed meats.

Grapefruit juice is responsible for another important food-drug interaction. Grapefruit juice contains flavonoids (naringin and naringenin) and furanocoumarin phenylpropanoids (bergamottin and 6', 7'-dihydroxybergamottin), which inhibit CYP3A4 in the intestine and liver.[48] This results in reduced metabolism of drugs that are eliminated by this isoenzyme. Bioavailability of these drugs may increase by 200%, leading to adverse drug effects.[48]

Medications affected by grapefruit juice include calcium channel blockers such as verapamil and the dihydropyridines (felodipine, nifedipine, nimodipine, nisoldipine, and nitrendipine), as well as the benzodiazepines (midazolam, triazolam). Also affected are the HMG-CoA reductase inhibitors (lovastatin and simvastatin more than atorvastatin), amiodarone, buspirone, cyclosporine, terfenadine, and quinine.[2,4,49]

Patients should avoid drinking grapefruit juice for two hours before and four hours after taking drugs in these categories. For extended-release preparations, the patient should wait until 6 hours have passed before drinking grapefruit juice.

Licorice has several important food-drug interactions. Licorice contains a saponin glycoside called glycyrrhizin, which inhibits 11-beta-hydroxysteroid dehydrogenase, the enzyme that converts cortisol to cortisone. Chronic ingestion of large amounts of licorice results in pseudohypoaldosteronism, with hypokalemia, muscle weakness, sodium and water retention, hypertension, and cardiac arrhythmias. Thus, licorice can interfere with the effectiveness of antihypertensive medications and worsen the hypokalemia that is associated with certain diuretics such as bumetanide, chlorothiazide, chlorthalidone, ethacrynic acid, furosemide, hydrochlorothiazide, metolazone, spironolactone, and torsemide. In addition, hypokalemia worsens the toxicity of digoxin. Licorice also decreases the effectiveness of warfarin and increases the risk of side effects for patients taking corticosteroid or estrogen therapy.[50]

Drug and Ethanol Interactions

Ethanol is known to cause a number of drug interactions, many of which may be severe or life-threatening.

A significant interaction occurs when ethanol is consumed with cocaine, resulting in the formation of an active metabolite known as cocaethylene. The half-life of cocaethylene is much longer than that of cocaine, resulting in prolonged toxicity. The metabolism of cocaine is inhibited, also prolonging and enhancing the effects of the parent compound.[51]

Other drugs interact with ethanol by inhibiting the enzyme acetaldehyde dehydrogenase. Normally, ethanol is metabolized to acetaldehyde by alcohol dehydrogenase and, subsequently, acetaldehyde is metabolized to acetic acid by aldehyde dehydrogenase. However, the inhibition of aldehyde dehydrogenase by another drug leads to the accumulation of acetaldehyde when ethanol is also consumed. This is the mechanism behind the disulfiram reaction, resulting in nausea, flushing, headache, and palpitations. Drugs known to cause this disulfiram-like reaction include certain cephalosporins, chloramphenicol, chlorpropamide, disulfiram, griseofulvin, metronidazole, and nitrofurantoin.[52]

A reaction also occurs when combining ethanol and tacrolimus.[53] A local skin reaction of flushing and irritation has been reported at the site of topical tacrolimus application when ethanol is also consumed.[54]

Other notable ethanol-drug interactions include enhanced antiplatelet effect with aspirin; increased incidence of hepatitis with isoniazid; increased metabolism of methadone; increased hypoglycemic effect of oral hypoglycemics; increased metabolism of phenytoin; increased blood ethanol concentration with cimetidine and ranitidine; increased vasodilation with vasodilators; and increased metabolism of warfarin.

Finally, ethanol is a central nervous system depressant, potentiating the effects of other sedating drugs such as antihistamines, antidepressants, antipsychotics, barbiturates, gamma-hydroxybutyrate, marijuana, muscle relaxants, opioids, and any other sedative-hypnotic agent or central nervous system depressant.

Table 6: Drug Interactions with Common Dietary Supplements

Supplement Name	Interaction
Caffeine	Found in many beverages Potentiates the effects of amphetamines and other sympathomimetics
Dong quai[36]	Has warfarin derivatives: Risk of bleeding[31]
Ephedra[55]	Potentiates effects of caffeine
Feverfew	Associated with bleeding when used with warfarin
Garlic	Inhibits platelet aggregation: Increased risk of bleeding with warfarin
Ginger	Thromboxane synthetase inhibitor and may also decrease platelet aggregation: Increased risk of bleeding
Ginkgo biloba[56]	Decreases activity of valproic acid and carbamazepine Potent inhibitor of platelet activating factor: Risk of bleeding with warfarin and NSAIDs
Ginseng[55]	Can potentiate bleeding when used with warfarin and NSAIDs Potentiates MAOI
St. John's wort[56]	Decreased anticancer drug concentrations (irinotecan, imatinib) Decreased antiretroviral concentration (indinavir, nevirapine) Decreased cyclosporine concentrations Decreased OCP activity P450 inducer; lowers levels of many medicines (indinavir, cyclosporine, digoxin, warfarin)[31] Serotonergic properties may cause serotonin syndrome with SSRI
Vitamin E	Warfarin potentiation

Drugs and Dietary Supplement Interactions

More than 50% of Americans take dietary supplements on a daily basis. Supplements include vitamins, minerals, amino acids, herbs, and botanicals. A memory aid to help remember a group of the most common supplements involved in drug interactions is those beginning with the letter "g": ginger, garlic, ginkgo, and grapefruit.[55]

Table 6 summarizes commonly used supplements in the United States and their reported interactions.[50]

Physician and Patient Education

Special attention should be paid when prescribing medications in the following settings:

- When the therapeutic effect of a drug is harmful in excess (or when it is insufficient) and the therapeutic margin is narrow, such as sulfonylureas, anticoagulants, CNS depressants, digoxin, and cytotoxic drugs;[2,11]
- When the drug produces altered receptor sensitivity in the autonomic nervous system, such as monoamine oxidase inhibitors, tricyclic antidepressants, antipsychotics, and cardiovascular medications;
- When over-the-counter medications, dietary supplements, and herbal remedies are used and self-prescription occurs;
- When several practitioners are providing care, especially when the medical record is not integrated and accessible to all;
- When combination medicines are prescribed by trade name.[2]

Patients should be educated about drug interactions and instructed to seek medical evaluation if symptoms occur.[11] Some useful patient tips provided by the Institute for Safe Medical Practices include:

- Read labels;
- Know drug warnings;
- Keep drugs in original containers;
- Ask your doctor about drug, food, and dietary supplement interactions;
- Ask your pharmacist before taking over-the-counter medications if you are taking a prescription medicine;
- Use one pharmacy for all your medicines;
- Inform all your doctors about all your medicines, including supplements;
- Keep a list of all your medicines, including supplements;
- Don't save medicines for future use;
- Don't share medicines;
- Don't double doses of medicines.

Physicians can decrease the risk

of drug interactions by selecting medication regimens that optimize therapeutic benefit while minimizing the risk of adverse drug events. Medications that are not essential should be eliminated, especially in high-risk patients who are taking multiple drugs. Physicians should keep informed of important drug interactions and be able to recognize the clinical presentation of drug interactions, which may mimic other disease states. It is important to use available resources such as Internet sites and computerized databases to help screen for drug interactions.

Many hospitals and pharmacies utilize clinical decision software. In at least in one study, these software programs did not perform well, but, nevertheless, they are useful tools, as they alert clinicians about potential drug interactions.[57]

Some pharmacy schools have increased the education of pharmacists about drug interactions, since pharmacists are a source of information for many physicians.[58] A study in the medical intensive care unit showed that having a clinical pharmacist during rounds decreased potential drug interactions by 65% and decreased length of stay. Mortality was not affected.[59]

Online resources are also helpful, especially when dealing with rapidly changing or dangerous drugs, such as in oncology and HIV. Finally, report all drug interactions to MedWatch or to the local Poison Control Center.[60] These are the best ways to identify and track drug interactions that may affect patient safety.

Conclusions

Drug interactions occur when the effects of a drug are modified by the concomitant administration of another substance, most commonly another prescription medication. However, serious drug interactions also occur with over-the-counter medications, foods, vitamins, dietary supplements, herbal products, alcohol, and illicit drugs. These adverse drug events are a common cause of morbidity and mortality, resulting in billions of dollars annually in additional health care costs.

The risk of drug interactions increases significantly with the number of medications used. Patients at increased risk of drug interactions include those taking multiple medications, especially the chronically ill, elderly, critically ill patients with organ compromise, children with special health care needs, and patients who consume over-the-counter, dietary, and herbal preparations.

Physicians need to educate themselves and their patients on the most common and the most deadly drug interactions. The use of computer software, pharmacists, online resources, and the Poison Control Center are all options that help reduce the probability of serious drug interactions.

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Physician CME Questions

1. Drug interactions are becoming more common because more patients are taking multiple medications daily. How many medications does the average American older than 55 years of age take on a daily basis?

   A. 1 to 3 drugs
   B. 3 to 5 drugs
   C. 6 to 9 drugs
   D. 10 to 15 drugs

2. What percentage of Americans older than 55 years of age are taking multiple drugs that can put them at risk of a significant drug interaction?

   A. 1%
   B. 4%
   C. 20%
   D. 75%

Emergency Medicine Reports

CME Objectives

Upon completion of this educational activity, participants should be able to:

- recognize specific conditions in patients presenting to the emergency department;
- apply state-of-the-art diagnostic and therapeutic techniques to patients with the particular medical problems discussed in the publication;
- discuss the differential diagnosis of the particular medical problems discussed in the publication;
- explain both the likely and rare complications that may be associated with the particular medical problems discussed in the publication.

3. Which of the following is one of the most commonly reported drug interactions seen in patients being evaluated in the emergency department?
   A. dizziness
   B. nausea
   C. quinidine-like effect
   D. QT prolongation

4. Which of the following metabolic pathways account for greater than 75% of a drug's metabolism?
   A. acetylation
   B. cytochrome p450
   C. glucuronidation
   D. sulfation

5. According to one study, the most common causes for hospitalization due to drug interactions include:
   A. gastrointestinal bleeding, vomiting, hypertension, bradycardia
   B. bradycardia, diarrhea, hypotension, long QTc
   C. bradycardia, hypertension, hypotension, vomiting
   D. gastrointestinal bleeding, hypertension, hypotension, and cardiac rhythm disturbances

6. Which of the following statements is true regarding drug interactions that prolong the QT interval of the electrocardiogram?
   A. Prolongation of the QT interval decreases the risk of ventricular dysrhythmias, including torsades de pointes.
   B. The risk of sudden death is increased when QT interval-prolonging medications are taken in combination.
   C. Hypokalemia is protective against development of torsades de pointes when QT interval prolongation is present.
   D. The azole antifungal agents (itraconazole, ketoconazole, miconazole) have not been associated with prolonged QT interval.

7. Which of the following foods or herbal supplements may precipitate serotonin syndrome when taken in combination with selective serotonin reuptake inhibitors (SSRI)?
   A. ginger
   B. garlic
   C. St. John's wort
   D. licorice

8. Which of the following statements is true regarding drug and ethanol interactions?
   A. Ethanol decreases the central nervous system depression of sedative hypnotic drugs.
   B. Consumption of ethanol with cocaine shortens the duration of cocaine toxicity.
   C. Ethanol decreases the antiplatelet effect of aspirin.
   D. Consumption of ethanol with certain medications such as griseofulvin or metronidazole may cause a disulfiram reaction.

9. Which of the following statements is true regarding the food-drug interactions?
   A. There are no known serious food-drug interactions.
   B. The patient's food consumption history is usually documented in the medical record.
   C. Foods containing tyramine can precipitate a life-threatening interaction with monoamine oxidase inhibitors (MAOI).
   D. Chronic licorice ingestion improves the hypokalemia associated with diuretic use.

10. What is the most common pharmacodynamic interaction involving warfarin?
   A. concomitant use with antibiotics
   B. concomitant use with anti-platelet medications
   C. concomitant use with diuretics
   D. concomitant use with opioids

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Dangerous Drug Interactions

Mechanisms of Drug Interactions

Interaction Type	Examples of Drug Interactions
Prior to IV administration	• Diazepam: Poor solubility • Precipitation of catecholamines with sodium bicarbonate
Prior to intestinal absorption	• Anticholinergics: slowed absorption • Antacids, histamine 2 blockers, and PPIs: Changes in pH can affect drug absorption (itraconazole, ketoconazole, and cefpodoxime) • Broad spectrum antibiotics: Eliminate vitamin K-producing bacteria in the gut (warfarin reaction) • Cholesterol resins (cholestyramine): Can bind other drugs and decrease their absorption (warfarin, digoxin, thyroid hormone, beta-blockers, thiazides, fibric acid drugs) • Metoclopramide: Hastens absorption
During intestinal absorption	• "First pass metabolism" and cytochrome 450 enzyme alterations
Protein binding	• Displacement from albumin and other proteins: • Warfarin and sulfonamide antibiotics • Diazepam displaces phenytoin from plasma proteins
Interactions at site of metabolism	• Due to p450 alterations; takes 4-6 weeks for peak effects • When induced, drug metabolism is exaggerated; when inhibited, drug metabolism is delayed
Interactions at site of secretion (renal)	• Probenecid decreases penicillin excretion • Salicylates and NSAIDs decrease methotrexate excretion • Cimetidine decreases metformin elimination • Indomethacin inhibits renal prostaglandins. This reduces renal blood flow and decreases drug elimination. • Changes in urine pH: Aspirin's excretion is enhanced by urine alkalinization
Pharmacodynamic interactions	• Antagonism: Drugs with opposing pharmacologic actions diminish the physiologic response • Agonism (synergism): Drugs with similar effects increase the physiologic response

Selected Drug Interactions with Warfarin

Increased Effect of Warfarin (Elevated INR)	Decreased Effect of Warfarin (Low INR)
Amiodarone Azole antifungals (fluconazole) Cephalosporins Cimetidine Ethanol Fluvastatin HMG-CoA reductase inhibitors (Lovastatin) Isoniazid Macrolides (clarithromycin, erythromycin) Metronidazole NSAIDs, acetaminophen, aspirin Quinolones (ciprofloxacin) Tricyclic antidepressants	Barbiturates Carbamazepine Cholestyramine Cigarette smoking Corticosteroids Oral contraceptives Phenytoin Primidone Rifampin St. John's wort Vitamin K

Selected Drug Interactions with Digoxin

Effect	Drugs
Increased serum levels	Amiodarone Benzodiazepines Cyclosporine Itraconazole Indomethacin Macrolides Omeprazole Propafenone Quinidine Tetracyclines Verapamil
Decreased serum levels	Albuterol Aminoglycosides (oral) Aluminum/magnesium antacids Activated charcoal Cholestyramine Rifampin St. John's wort Sulfasalazine
Enhanced pharmacodynamic effects	Beta-blockers Calcium channel blockers Cyclosporine Diuretics Sympathomimetics
Antagonize pharmacodynamic effects	Thyroid hormone

Drugs that Prolong the QT Interval

Drug Family	Drug Family
Antiarrhythmics 1A: disopyramide, procainamide, quinidine 1C: flecainide, encainide III: amiodarone, ibutilide, sotalol	Azole antifungals (ketoconazole, miconazole, itraconazole)
Antidepressants (tricyclics, SSRIs, lithium)	Calcium channel blockers (diltiazem, verapamil)
Antihistamines (astemizole, diphenhydramine, hydroxyzine, terfenadine)	Protease inhibitors
Antimicrobials (amantadine, quinine, chloroquine, ciprofloxacin, macrolides, pentamidine)	Others: Arsenic Cisapride Methadone Organophosphates Vasopressin
Antipsychotics (chlorpromazine, droperidol, haloperidol, ziprasidone)	

Selected Drugs that Increase Serotonergic Activity

Antidepressants (trazodone, venlafaxine, mirtazapine)	MAOIs (phenelzine, moclobemide, clorgyline, isocarboxazid)
Cocaine, amphetamines	Meperidine
Dextromethorphan	St. John's wort (hyperforin)
L-tryptophan	SSRIs (fluoxetine, citalopram, paroxetine, fluvoxamine, sertraline)
Linezolid (weak MAOI)	Pentazocine
Lithium	Triptans
LSD	Tramadol

Drug Interactions with Common Dietary Supplements

Supplement Name	Interaction
Caffeine	Found in many beverages Potentiates the effects of amphetamines and other sympathomimetics
Dong quai	Has warfarin derivatives: Risk of bleeding
Ephedra	Potentiates effects of caffeine
Feverfew	Associated with bleeding when used with warfarin
Garlic	Inhibits platelet aggregation: Increased risk of bleeding with warfarin
Ginger	Thromboxane synthetase inhibitor and may also decrease platelet aggregation: Increased risk of bleeding
Ginkgo biloba	Decreases activity of valproic acid and carbamazepine Potent inhibitor of platelet activating factor: Risk of bleeding with warfarin and NSAIDs
Ginseng	Can potentiate bleeding when used with warfarin and NSAIDs Potentiates MAOI
St. John's wort	Decreased anticancer drug concentrations (irinotecan, imatinib) Decreased antiretroviral concentration (indinavir, nevirapine) Decreased cyclosporine concentrations Decreased OCP activity P450 inducer; lowers levels of many medicines (indinavir, cyclosporine, digoxin, warfarin) Serotonergic properties may cause serotonin syndrome with SSRI
Vitamin E	Warfarin potentiation

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