Strategies for Avoiding Drug-Drug Interactions in Urgent Care

Urgent message: With the increasing number of drugs on the market, patients are more and more likely to be taking multiple medications. Urgent care providers need to be alert for potential interactions when changing or adding to a patient's drug therapy.

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Consider This Patient Scenario:

A 28-year-old woman who says she is a traveling nurse currently on an assignment at a nearby hospital presents to an urgent care clinic with a complaint of frequency, urgency and burning on urination. She is going on a ski trip and wants to ensure that she clears up what she believes is a urinary tract infection (UTI) before leaving on vacation. The patient denies vomiting but complains of intermittent nausea. She denies flank pain, vaginal discharge, and the possibility of pregnancy. Interestingly, the woman does tell the provider that she was on birth control pills (BCPs) but developed a blood clot in her thigh and then a pulmonary embolism (PE) after flying cross country. She has been on warfarin for the past 3 months and her last International Normalized Ratio (INR) (yesterday) was 2.4. Also noteworthy is that the woman has had a significant reaction to penicillin-based antibiotics in the past.

The urgent care provider orders a urinalysis (UA) and urine chorionic gonadotrophin (UCG) test. On examination, the patient's vital signs are as follows:

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BP 120/72
P 88
R 16
T 39.2
Pain Scale 4/10.

TABLE 1. Overview of Deleterious Drug-Drug Interactions*

	Concomitant Drug	Potential Effect	Recommendations
Warfarin	Azithromycin, ciprofloxacin (Cipro), clarithromycin (Biaxin), erythromycin, metronidazole (Flagyl) and TMP-SMX (Bactrim, Septra)	Increased effect of warfarin	Select alternative antibiotic
	Acetaminophen	Increased bleeding, increased INR	Use lowest possible acetaminophen dosage and closely monitor INR
	Acetylsalicylic acid (aspirin)	Increased bleeding, increased INR	Limit aspirin dosage to 100 mg/day and closely monitor INR
	NSAID	Increased bleeding, increased INR	Avoid concomitant use if possible; if unavoidable, use a cyclooxygenase-2 inhibitor and closely monitor INR
Fluoroquinolone	Divalent/trivalent cation	Decreased absorption of fluoroquinolone	Space administration by 2 to 4 hours
	Theophylline	Increase in theophylline serum concentration	
Oral Contraceptives	Rifampin	Decreased effectiveness of OC	Recommend alternative method of contraceptive
	Carbamazepine, Felbamate, Oxcarbazepine, etc	Decreased effectiveness of OC	Choose alternative AED
Statins	Warfarin	Increased effect of warfarin	Monitor INR
	Gemfibrozil	Possible rhabdomyolisis	Avoid if possible
	Erythromycin, clarithromycin	Increased levels of simvastatin and lovastatin	Avoid if possible
Fluoxetine	Clozapine, lithium and olanzapine	Increased levels of concomitant drugs	
Citalopram	Monoamine oxidase inhibitors	Serotonin syndrome	
Paroxetine	Warfarin	Increased bleeding	Avoid if possible

INR = International Normalized Ratio; NSAID = nonsteroidal anti-inflammatory drug; OC = oral contraceptive; TMP-SMX = trimethoprim sulfamethoxazole
***Adapted** from http://www.aafp.org/afp/2000/0315/p1745.html

The woman's exam is unremarkable, other than some slight suprapubic tenderness. Her urine dipstick comes back with 4+ leukocytes and is nitrite positive and her UCG is negative.

She is appropriately diagnosed with a UTI. Noting the patient's allergy to penicillin, the provider prescribes trimethoprim and sulfamethoxazole (TMP-SMX) and pyridium and discharges the patient home.

A few days later, sadly, the patient was flown into a trauma center in Denver unresponsive after a seemingly minor head injury, which occurred during a snowboarding accident while she was wearing a helmet. On admission, the woman's Glasgow Coma Scale score was 3 and her INR was 8.2. Computed tomography scan revealed a massive epidural hematoma causing herniation. Her family removed her from life support after donating her organs.

The Rise of Drug-Drug Interactions

In 2012, the FDA approved 35 new medications [1], and interactions between medications have been increasingly reported.[2] As patients' medication lists become longer and the use of multiple drug therapies becomes more frequent, it is increasingly important for the provider to consider drug interactions and question the safety of drug regimens. Among other risk factors, the frequency of drug-drug interactions increases most significantly with the number of medications in use. Adverse drug events, including drug-drug interactions, account for 19% of all hospital injuries[3] and most involve commonly-used medications. By underscoring the potential for drug interactions with warfarin, as illustrated by the patient scenario above, this article highlights the importance of recognizing drug-drug interactions and considering the factors that increase their risk.

Drug Interactions with Warfarin

Warfarin is the anticoagulant most widely prescribed in North America[4] and interactions leading to over-anticoagulation, under-coagulation, or increased bleeding are well described for an increasingly large number of drugs taken concomitantly. Warfarin and other vitamin K antagonists (acenocoumarol, phenprocoumon, fluindione) are prescribed as oral anticoagulants for thrombosis prophylaxis in many clinical settings. This class of drugs act by inhibiting the synthesis of vitamin K, a vitamin necessary for activation of coagulation factors. Warfarin is known to have a narrow therapeutic range and dose response and resultant INR vary greatly between individuals. Especially notable are the interactions between warfarin and antibiotics, acetaminophen, aspirin, and nonsteroidal anti-inflammatory drugs (NSAIDs) (**Table 1**).

For urgent care providers, obtaining a thorough history is the best way to prevent poor outcomes due to unforeseen drug-drug interactions. It is important to review medication lists and consider possible drug-drug interactions before prescribing new medications to patients using warfarin.

Antibiotics

By reducing vitamin K levels in the gut flora, antibiotics can heighten the effects produced by warfarin, leading to over-anticoagulation.[5] Another mechanism recognized for increased bleeding with warfarin is inhibition of its metabolism. Drugs that have been found to inhibit warfarin metabolism include azithromycin, ciprofloxacin (Cipro), clarithromycin (Biaxin), erythromycin, metronidazole (Flagyl) and TMP-SMX (Bactrim, Septra).[2]

Upon its release in 1993, azithromycin was originally believed to be free of interaction with warfarin. However, in 2009, the FDA revised its label on the package insert to read, "Although, in a study of 22 healthy men, a 5-day course of azithromycin did not affect the prothrombin time from a subsequently administered dose of warfarin, spontaneous post-marketing reports suggest that concomitant administration of azithromycin may potentiate the effects of oral anticoagulants. Prothrombin times should be carefully monitored while patients are receiving azithromycin and oral anticoagulants concomitantly."[6]

In a population-based cohort study of patients using acenocoumarol or phenprocoumon, several antibiotics strongly increased the risk of over-anticoagulation; 351 of the 1,124 patients in the cohort developed an INR of 6.0.[7] In the study, TMP-SMX was associated with the greatest risk of over-anticoagulation.[7] Given these findings, urgent care providers should select an alternative antibiotic that has not been implicated in over-anticoagulation for patients who are taking warfarin.

Acetaminophen

Acetaminophen is the most frequently ingested medication in the United States[2] and it has been recognized as another cause of over-anticoagulation. In one study, high doses of acetaminophen (9100 mg/week or just 3 extra-strength tablets per day) were found to be associated with a 10-fold increased risk of having an INR > 6.0.[8] In a case report, acetaminophen was found to enhance the effect of warfarin but the elevation may only be apparent after a few days of acetaminophen therapy.[9]

Nonsteroidal Anti-Inflammatory Drugs

Concomitant use of NSAIDs and warfarin increases risk of bleeding and should be avoided. However, in a study assessing rates of hospitalization for gastrointestinal bleeding, the selective cyclooxygenase-2 (COX-2) inhibitors celecoxib (Celebrex) and rofecoxib (Vioxx) were preferable to nonselective NSAIDs in patients who required NSAIDs.[10] COX-2 inhibitors have reduced antiplatelet properties compared with nonselective NSAIDs.

Also noteworthy is that the particular need to avoid use of nonselective NSAIDs in patients who are at increased risk of NSAID gastropathy. Factors including age > 65, history of peptic ulcer disease, exposure to systemic steroid therapy, heavy smoking, or high usage of NSAIDs are red flags for heightened risk of gastropathy.[2]

Counseling patients about the risks of bleeding associated with concomitant therapy with warfarin and NSAIDs and close monitoring of INR values are important to minimize risk of bleeding.

Monitoring INR Values

According to *UpToDate*, the guidelines for returning INR values to the patient's normal range are as follows:

- INR <5.0 without bleeding: If the INR is above normal range but less than 5.0 with no significant bleeding, it is recommended that the next dosage of warfarin be omitted or the maintenance dose be reduced.[11]
- INR 5.0-9.0 without bleeding: If there is no significant bleeding, there is approximately a 1% risk of a major hemorrhage occurring in the next 30 days. Two of the options for reducing INR values are:
  a. Stopping warfarin temporarily.
  b. Stopping warfarin temporarily and adding a dose

of 1 to 2.5 mg of oral vitamin K. This is a faster approach to correct excessive anticoagulation.[11]

- INR >9.0 without bleeding: If there is no significant bleeding with these INR values, warfarin should be omitted and 2.5 to 5 mg of oral vitamin K should be administered. INR values should be closely monitored for 24 to 48 hours and vitamin K treatment should be repeated as necessary.[11]
- Elevated INR with minimal bleeding: Although there are no precise guidelines for this situation, the decision is based upon clinical judgment, INR level, and current extent/risk of worsening of the bleeding. Providers may choose to follow treatment plans for INR >9.0 without bleeding, or opt for more emergent care depending on the severity of the case.[11]

Drug Interactions with Antibiotics

Fluoroquinolones

Antibiotics can interact with other drugs via multiple mechanisms; this article highlights significant interactions involving the fluoroquinolone class of antibiotics. Agents containing divalent cations and trivalent cations can reduce absorption of fluoroquinolones through creation of insoluble complexes in the gut, which results in failure of treatment. Cations are present in many medications and over-the-counter products, and it has been found that absorption of fluoroquinolones is reduced by 60% to 70% when they are taken concomitant with products containing divalent or trivalent cations.[2]

The divalent cation calcium is present in Caltrate, Citracal, Os-Cal, PhosLo, Titralac, and Tums, whereas the divalent cation magnesium is found in Almora, Citrate of Magnesia, Mag-Ox 400, Milk of Magnesia, Slow-Mag, and Uro-Mag. Aluminum and ferrous sulfate are trivalent cations that can be found in Alu-Cap, AlternaGel, Amphojel, Basalje and Feosol, Fergon, Niferex, Nu-Iron, and Slow Fe, respectively.[2]

Ciprofloxacin, enoxacin, lomefloxacin, norfloxacin, and ofloxacin are affected by divalent and trivalent cations found in antacids. Sucralfate, containing the trivalent cation aluminum, has been found to inhibit

absorption of several quinolones, including ciprofloxacin and norfloxacin.[12]

It is important to advise patients to stop taking products containing divalent or trivalent cations until their fluoroquinolone therapy has ceased.[2] It has been shown that inhibition of absorption can be avoided by administering the antibiotic at least 2 hours before or 6 hours after the cation.[12]

Theophylline

Quinolones inhibit metabolism of theophylline, which results in an increase in theophylline serum concentrations and subsequent reactions, leading to tachycardia, nausea, and seizures.[12] Quinolone antibiotics exhibit a wide range of inhibition: Enoxacin can result in a 65% reduction of theophylline clearance whereas ciprofloxacin inhibits by about 30%. Norfloxacin, ofloxacin, and lomefloxacin have been found to produce only a minimal effect.[12]

Patients with the upper normal limits of theophylline serum concentrations are more likely to develop these types of effects.[12] This is an important factor to consider when determining whether the addition of a quinolone is advisable. Note: It can take 2 to 3 days after the combination of quinolone and theophylline for the effects to become pronounced, therefore, patients should be monitored for signs and symptoms of toxicity.

Drug Interactions with Oral Contraceptives

Antibiotics

Clinical studies have not been demonstrative of a consistent effect of antibiotics on the decreased effectiveness of oral contraceptives (OCs), and concomitant use is debatable. Given the low frequency of this drug-drug interaction, it is difficult to differentiate a pregnancy due to the antibiotic from the expected failure rate.[2] Rifampin can impair the effectiveness of OCs because of its ability to increase activity of hepatic enzymes, which are involved in estrogen metabolism.[2] Concomitant use of rifampin and OCs can lead to breakthrough bleeding and potentially an increased risk of pregnancy.

Although pharmacokinetic studies of other antibiotics such as tetracycline and penicillin derivatives have not shown any systematic interactions with OCs, individual patients have been found to have decreased plasma concentrations of ethinyl estradiol. It is theorized that any interaction between OCs and antibiotics may involve ethinyl estradiol.

An analysis of 167 articles on drug interactions between antibiotics and OCs resulting in contraceptive failure found that approximately 20% of women reporting to family planning or abortion clinics were taking antibiotics and OCs concomitantly.[13] However, a retrospective study of 365 patients who were co-administered OCs and an antibiotic showed only a small but insignificant increase in risk of pregnancy.[2]

According to the American College of Obstetricians and Gynecologists Committee Opinion on medical eligibility criteria for contraceptive use, there is no restriction on use of OCs with broad spectrum antibiotics, antifungals, or antiparasitics. However, with regards to rifampicin or rifabutin therapy, the risk of pregnancy was found to outweigh the advantages of using OCs as a birth control method.[14]

Take home point: Concomitant use of broad spectrum antibiotics and OCs is considered to be a safe practice. However, urgent care providers may want to encourage patients on OCs to use back-up contraception during rifampicin therapy.

Antiepileptic Drugs

Prescription of OCs to women with epilepsy is fairly common, despite the knowledge that concomitant use may reduce the pill's efficacy.[15] Antiepileptic drugs (AEDs) that have been shown to induce metabolism of the steroidal components of the pill include carbamazepine, felbamate, oxcarbazepine, lamotrigine, phenobarbital, phenytoin, primidone, and topiramate.

However, the magnitude of interaction depends on the dosage of the AED. For example, topiramate does not affect serum norethisterone and ethinyl estradiol levels at dosages up to 100 mg per day but decreases serum norethisterone consistently at higher doses.[15] Likewise, carbamazepine 600 mg per day reduces serum levels by 50%. Gabapentin, levetiracetam, pregabalin, tiagabine, valproate, vigabatrin, and zonisamide have not been reported to interact with steroid OCs.[15]

Take home point: the best way to avoid complications with this drug-drug interaction is to choose an AED that is not known to interact with OCs.

Drug Interactions With 'Statins'

Statins are effective in treatment of hypercholesterolemia because of their ability to reduce low-density lipoprotein cholesterol levels. However, there are many drugs that create adverse reactions when taken concomitant with statins; generally, the risk of drug-drug interactions is dose-dependent. Because of the likelihood that patients receiving statin therapy are elderly and may be on multiple other drugs for comorbid conditions such as heart disease or

hypertension, it is especially important to be aware of statin-drug interactions in these situations.

Drugs that raise statin concentrations in the blood and can increase risk of adverse interactions such as myopathy include immunosuppressant drugs, macrolides, fibrates, protease inhibitors, azole antifungals, warfarin, and digoxin.[16] For example, one study reported myopathy incidence of 2%, 5% and 28% in patients receiving lovastatin therapy with niacin, gemfibrozil and cyclosporine plus gemfibrozil, respectively.[16] It is important to be aware of CYP3A4 inhibitors when considering co-administration; a systematic review of statin safety including data from 20 randomized controlled trials showed that 60% of cases of rhabdomyolysis in patients receiving simvastatin, lovastatin or atorvastatin involved co-administration of CYP3A4 inhibitors, and 19% involved co-administration of fibrates.[16]

General Interactions

Verapamil and diltiazem have been shown to increase simvastatin plasma concentration up to fourfold, and diltiazem was also found to have the same effect with concomitant lovastatin therapy.[16] Statin drug-drug interactions with warfarin are well documented, and an elevated INR is a concern with warfarin and various statins (fluvastatin, lovastatin, and simvastatin). Antibiotics that are CYP3A4 inhibitors, such as erythromycin and clarithromycin, have been reported to increase plasma concentration of simvastatin and lovastatin. Conversely, the antibiotic rifampicin has been demonstrated to decrease plasma levels of statins including atorvastatin, simvastatin, pravastatin, and fluvastatin.[16] Azole antifungal drugs, such as itraconazole and etoconazole, have been shown to increase the availability of atorvastatin, simvastatin, lovastatin, and rosuvastatin.[16]

Fibrates

Of special importance is the recognition of fibrate-statin interactions. Gemfibrozil has been shown to interact with atorvastatin, simvastatin, lovastatin, pravastatin, and rosuvastatin. However, bezafibrate,

TABLE 2. Antibiotic Choices for Patients on Warfarin

Presentation	Recommendations
Community Acquired Pneumonia	• Cefuroxime axetil (Ceftin) 250-500 mg twice daily • Ceftriaxone (500 mg twice daily) *
Urinary Tract Infection	• Nitrofurantoin 100 mg orally twice daily for 5 days • Fosfomycin trometamol 3 g orally in single dose • Cefaclor 250 mg every 8 hours (as capsules or oral suspension)
Otitis Media	• Cefaclor 250 mg every 8 hours (as capsules or oral suspension)
Pharyngitis	• Clindamycin 7 mg/kg orally three times daily (300 mg maximum dose) for 10 days
Bacterial Vaginosis	• Clindamycin cream 2% one full applicator (5 g) intravaginally once daily for 7 days
Cellulitis	• Clindamycin 300-450 mg orally 3 times daily • Linezolid 600 mg orally twice daily (pediatric dose 10 mg/kg orally every 8 hours, maximum 600 mg/dose)

*The elevation of INR due to concomitant warfarin therapy and Ceftriaxone treatment has only been documented in a single case study in 2011[18]; frequent INR monitoring is recommended.
Important factors to consider when reviewing the medication list include the patient's age, the dosage of medications, and his/her usage of antibiotics.

clofibrate and fenofibrate have also been implicated in cases of rhabdomyolysis when combined with statins. Because of the well-documented dangerous interactions with fibrate, statin-fibrate combination therapy should be reserved for patients with severe hyperlipidemia.[16] In addition, it is also important to consider other factors, such as age, gender, diabetes, and hypothyroidism that may make a patient more susceptible to statin-induced myopathy.

Drug-drug interactions with statins are extensive, and only a few examples have been highlighted in this review. Take care in co-administering statins with the drugs mentioned above: immunosuppressant drugs, macrolides, fibrates, protease inhibitors, azole antifungals, warfarin, and digoxin.

Interactions With the 'New Generation' of SSRIs

Drug interactions with tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs) have been well documented. Since the advent of selective serotonin reuptake inhibitors (SSRIs), newer classes of antidepressants have been widely adopted due to their relative safety compared with previous antidepressants. Even though SSRIs are reportedly safer than the "first generation" of antidepressants, drug-drug interactions are still an issue because of metabolism by the cytochrome 450 system in the liver. The concomitant use of SSRIs and drugs that are also metabolized by this system can lead to increased serum levels of these drugs. This article will highlight the recently documented interactions with the "new generation" of SSRIs, including fluoxetine, citalopram, and paroxetine.

Fluoxetine

Fluoxetine (FLU) has a long half-life (1-4 days) and, for that reason, it has a high risk of interacting with other drugs. Plasma levels can be significant even weeks after discontinuation of FLU therapy, so care should be taken with administration of any new drug to a patient taking FLU. Increased plasma levels of clozapine, lithium, and olanzapine have been observed with co-administration. In addition, FLU increases the half–life of diazepam. FLU has also shown to be an inhibitor of MAO enzymes, therefore, care should be taken when considering co-administration with MAOIs.[17]

Citalopram

Citalopram is used to treat symptoms of major depression and it is also being evaluated in treatment of some anxiety disorders. Concomitant use of antifungal medications and erythromycin can increase levels of citalopram. In addition, administration of citalopram with MAOIs can cause serotonin syndrome, characterized by at least three of the following symptoms: diarrhea, fever, sweating, mood or behavior changes, overactive reflexes, fast heart rate, restlessness, shivering or shaking.[17]

Paroxetine

Paroxetine is probably the most selective SSRI, relatively safe regarding cardiovascular effects, and is often used in elderly patients. About 95% of absorbed paroxetine is bound to plasma proteins, making interactions with other bound drugs such as clozapine and oral anticoagulants likely. Trials have shown an increase in bleeding after prolonged co-administration of paroxetine and warfarin.[17]

The prevalence of multiple chronic medical conditions requiring many different therapeutic protocols increases with old age, amplifying the chance of adverse drug-drug interactions.

Patient History

A detailed history is the most effective way to prevent drug-drug interactions. Often, in the urgent care setting, it is difficult to obtain the entirety of a patient's medical record. A thorough history can help prevent gaps in the medical record. Important factors to consider when reviewing the medication list include the patient's age, the dosage of medications, and his/her usage of antibiotics. Although the urgent care provider in the patient scenario above appropriately prescribed an antibiotic other than penicillin because of the patient's allergy, he did not recognize the interactions between warfarin and antibiotics. It is just as important to be aware of potential drug-drug interactions to avoid preventable complications. **Table 2** suggests alternative antibiotics for common urgent care presentations in patients on warfarin therapy.

Age

Age is an important factor to consider in prevention of drug-drug interactions. Factors including frailty, memory loss, and use of many medications all contribute to the increased incidence of drug-related issues in older individuals.[19] The prevalence of multiple chronic medical conditions requiring many different therapeutic protocols increases with old age, amplifying the chance of adverse drug-drug interactions.

Dosage

Adverse drug events, including dangerous drug-drug interactions, are commonly dose-related. To prevent dosage-related drug interactions, it is important as a provider to be aware of a number of factors that con-

tribute to drug maintenance, including a patient's nutritional status, degree of compliance, hepatic and renal function, and potential genetic factors contributing to the individual's response to a particular drug.[20]

Conclusion

With the increasing number of drugs on the market and the prevalence of lengthy medication lists, it is unrealistic to expect an urgent care provider to remember all potential drug interactions. However, it is necessary to maintain a high level of suspicion when making changes or additions to a patient's medications. Care must be taken to thoroughly review existing medications—both conventional and nonconventional—when prescribing a new medication. Extra precautions should be taken when treating elderly patients who may be on multiple drug therapies. ■

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