Drug Interactions:
Coping With Chaos!

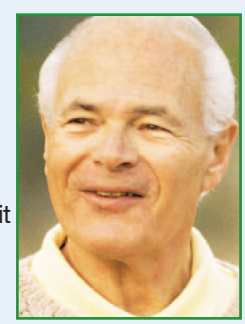
Kevin Pottie, MD, MCISc, CCFP; and Sheri Koshman, BSc Pharm

As presented at the Family Medicine Forum,
Montreal, Quebec

Drug interactions represent a prevalent, but often unrecognized cause of patient morbidity. In the emergency department, 3% to 30% of visits are related to adverse drug reactions and interactions.[1,2] As new drugs continue to emerge, family physicians face a formidable task in coping with the reality of drug interactions.

This article presents a technology-enabled, practical approach to drug interactions that emphasizes the identification of high-risk patients and high-risk drugs. This approach can also assist physicians in determining clinical significance and the importance of drug selection, monitoring, and patient education.

Ryan's case



Ryan, 60, is semi-retired and physically active, with poorly controlled hypertension (currently 190/100 mmHg). His medical history includes a body mass index of 25, osteoarthritis of the knees, and daily ingestion of grapefruit juice since giving up alcohol. He has a normal creatinine and an unremarkable echocardiogram.

He is taking:

- Ramipril, 20 mg once daily
- Naproxen, 500 mg twice daily
- Atenolol, 50 mg once daily
- Hydrochlorothiazide, 25 mg once daily
- Amlodipine, 10 mg once daily.

How would you manage Ryan's hypertension?
For a followup, see page 78.

What's involved in drug interactions?

There are four basic types of interactions that can lead to an adverse reaction:

1. Drug/drug;
2. Drug/food;
3. Drug/ethanol/tobacco; and
4. Drug/lab interactions.

Table 1
Characteristics of high-risk patients

- Elderly
- Chronic and multiple medical problems
- Cardiac problems
- Epilepsy
- Mental illness
- Transplant recipients
- HIV
- Excessive alcohol consumption
- Grapefuit juice consumption
- Herbalists

HIV: Human immunodeficiency virus

The main focus of this article will be drug/drug interactions (see Hansten, 1998 for an excellent clinical pharmacology review of drug interactions).[3]

How can you recognize a potential problem?

All patients are at risk for adverse drug interactions, however, certain patients stand out as high-risk (Table 1). Physicians should check for possible drug interactions when prescribing new medications for high-risk patients or when these patients present with symptoms suggestive of adverse drug reactions.

Polypharmacy occurs in 73% of patients over 65 and the estimated risk of drug interactions increases exponentially with the increase in medications. Frail, elderly patients are at particularly high risk (Table 2).

Table 2
Reasons elderly patients are at high risk for drug interactions

- Frequently suffer from multiple chronic illnesses and are on several medications
- May have impaired hepatic or renal function, resulting in altered drug metabolism or drug clearance
- May have impaired cognitive function, leading to medication errors
- More prone to adverse reactions and hospitalization linked to drug-related problems

Patients taking cardiovascular drugs are also at high risk for drug interactions (*e.g.*, risk of atrioventricular block with the combination of centrally acting calcium channel blocker and beta blocker, or the risk of renal impairment secondary to the interaction of non-steroidal anti-inflammatory drugs [NSAIDs] and angiotensin-converting enzyme [ACE] inhibitors).

Certain medications should also be considered at increased risk for drug interactions (Table 3). The efficacy and toxicity of drugs with low therapeutic indices (*e.g.*, lithium and warfarin) are often a cause for concern when there is an alteration of the metabolism and excretion environment. As well, patients who take herbal medica-

Dr. Pottie is an assistant professor, department of family medicine, University of Ottawa, and a family medicine practitioner, Ottawa, Ontario.

Ms. Koshman, a clinical pharmacist, Ottawa Hospital, is now a Pharm D student at the University of British Columbia, Vancouver, British Columbia.

Table 3
Characteristics of high-risk drugs

- Narrow therapeutic index (*e.g.*, warfarin, digoxin, theophylline, phenytoin, lithium)
- Metabolism
  - *Inhibitors:* Macrolides, azole antifungals, protease inhibitors
  - *Inducers*: Rifampin, phenytoin, CBZ, barbiturates
- Psychoactive drugs

CBZ: Carbamazepine

tions or follow certain diet regimens (*e.g.,* those who drink grapefruit juice) are also at higher risk of developing drug interactions.

What is the practical approach?

Our practical approach to coping with drug interactions (Figure 1) begins with identifying high-risk patients and high-risk drugs. Practice populations will vary, so we suggest using our lists as a starting point in identifying patients that may require a more focused review of medications. Patients at risk should then undergo a review of medications that should include a drug interaction screen. New technology greatly enables such screening. These technologies are:

- *Palm-based ePocrates R_x® 6.0*, which can be downloaded free from the Internet. ePocrates R_X Pro™ includes food and herbal medicine interactions, as well as calculation programs, but has a user fee.

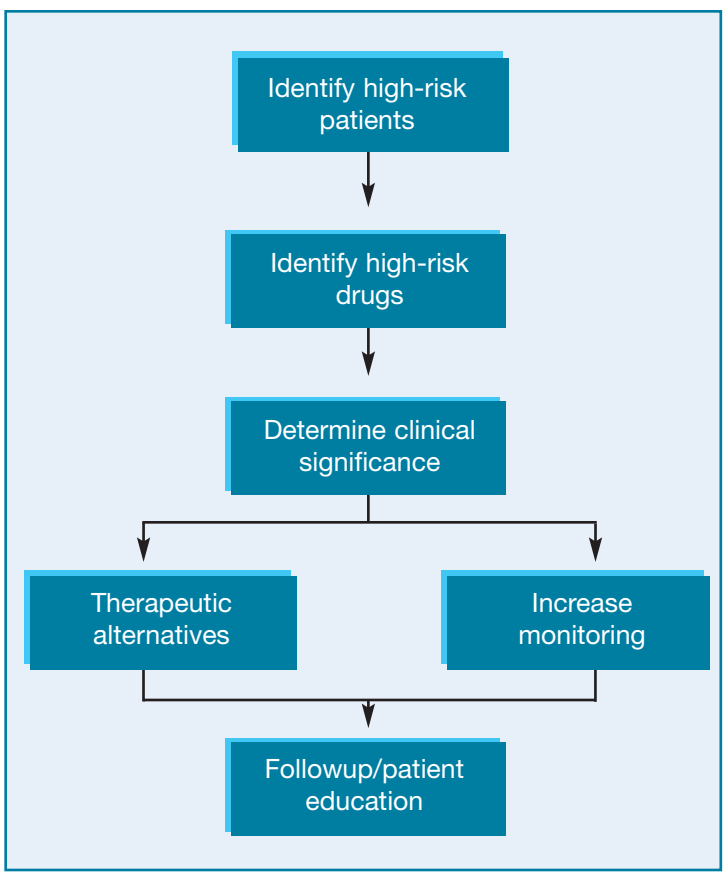


Figure 1. Practical approach to coping with drug interactions.

A followup on Ryan

Applying a practical approach to Ryan's case reveals that the non-steroidal anti-inflammatory drug (NSAID)/angiotensin-converting enzyme inhibitor combination is putting him at risk for renal toxicity and hampering his blood pressure control. The risk of complete heart block, a problem when beta blockers are mixed with centrally acting calcium channel blockers (*i.e.*, diltiazem) is not a problem with amlodipine. Grapefruit juice should generally be discouraged in patients taking amilodipine.

Rather than increasing his atenolol, which could decrease his exercise tolerance, the treatment approach could include stopping his NSAID, substituting acetaminophen or capsaicin for his osteoarthritis, informing him of the risk of grapefruit juice, and following up on his blood pressure and creatinine.

In Ryan's case, simply stopping the NSAID led to a decrease in blood pressure.

- *Micromedex*™
- *Drug-Facts and Comparisons: Drug Interactions,* which is available as a hard copy, in a modified PDA version, on a CD, or online (*www.factsandcomparisons.com*). It is not a free service.

The physician can use the screening results to help determine the clinical significance of the risk and then to make appropriate substitutions or increase monitoring interventions.

In many cases, the risk of adverse drug interactions can be mitigated by educating patients concerning risks or increasing the frequency of monitoring. For example, if there is some concern regarding warfarin interactions, increase the frequency of international normalized ratio monitoring. The onset of drug interactions can be immediate or delayed and the severity can vary among patients. The evolving world of drug therapeutics and the reality of patient idiosyncrasies emphasize the need for an approach that allows for clinical suspicion and regular monitoring.

What are the advantages?

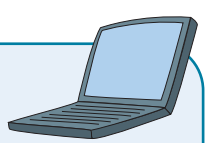
This approach focuses on the process of technology-enabled medication screening and the importance of links to updated drug information resources. If done regularly, this process offers an opportunity for practice-based learning.

What are the disadvantages?

The main disadvantage of this approach is its reliance on technology and the risk that it oversimplifies the task of watching for adverse drug reactions in practice. Drug interaction technology has been criticized for a focus on theoretical, as opposed to clinically significant interactions, over-reliance on clinical experience and case reports, and the extrapolation of interactions from one class to the whole class.

It is important that physicians apply critical thinking during the medication screening process so that if the risk identification or the technology fails, the physician will have the knowledge to appropriately address the risk of drug interactions.

Surf your way to...



Health Canada (for adverse drug reaction alerts):
www.hc-sc.gc.ca

Take-home message

What is a practical approach to dealing with drug interactions?

- When prescribing new drugs, physicians should check for possible interactions. Certain patients and certain drugs have higher risk of drug interactions (Tables 1 and 3).
- With a focus on high-risk patients and drugs, technological tools, such as the ePocrates R_x Pro™, can be used to determine the clinical significance and risks of certain drug interactions.
- Developing relationships with pharmacists, contacting drug information centres, and watching for adverse drug interaction alerts on the Health Canada Web site are also helpful tools.

Helpful hints

Other helpful tips to decrease adverse drug interactions and to facilitate ongoing learning are:

- Developing a collaborative relationship with a community pharmacist;
- Contacting drug information centres; and
- Watching for adverse drug interaction alerts. Dx

References
1. Hohl CM, Dankoff J, Calacone A, et al: Polypharmacy: Adverse drug-related events, and potential adverse drug interactions in elderly patients presenting to an emergency department. Ann Emerg Med 2001; 38(6):666-71.
2. Tafreshi MJ, Melby MJ, Kaback KR, et al: Medication-related visits to the emergency department: A prospective study. Ann Pharmacother 1999; 33(12):1252-7.
3. Hansten PD: Understanding drug interactions. Science and medicine 1998; S(1):16-24.