19 The Pharmacoepidemiology of Drug Interactions: Why and How They Are Important

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Abstract
This chapter discusses the pharmacoepidemiology of drug–drug interactions—how, why, and when clinicians encounter DDIs.

When contemplating the drug-drug interaction (DDI) universe, four questions naturally arise: Are DDIs important? Is this something I actually need to worry about? In what ways might I encounter DDIs in my practice? How do I begin to identify and deal with them?

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The answers to the first two questions are easy: Yes, you **do** have to worry about this and yes, DDIs **are** important because they are part and parcel of a major public health initiative—the enhancement of patient safety and welfare by the elimination of medical errors.

Drug safety is a significant component of the overall patient safety movement. This in turn is based on the science of pharmacoepidemiology—the study of the use and effects of drugs in large numbers of people. One focus of pharmacoepidemiology is the study of adverse effects suffered by patients when they use therapeutic drugs.[1] These adverse effects can result from medication errors, adverse drug reactions, and adverse drug events. None of these terms precisely defines a DDI in the sense we are using it in this book. DDIs are not a subset of adverse drug reactions, rather if DDIs are severe enough and/or go unremedied, they become the *cause* of them.

For a number of reasons, the epidemiology of DDIs is complex and the true incidence of DDIs remains unknown.[2–5] Fortunately, we are learning about the incidence of adverse drug reactions and adverse drug events and it is often possible to infer what proportion of these are DDI-related.[6]

Adverse drug reactions and adverse drug events are common, costly, and cause a significant morbidity and mortality.[7,8] For example, in 2007, the Institute of Medicine estimated that between 380,000 and 450,000 preventable adverse drug reactions occur annually.[9] It has been reported that an estimated 5.3% of hospital admissions were due to an adverse drug reaction.[10,20] Adverse drug reactions are also costly: A 1997 study reported that an adverse drug reaction increased the cost of a hospitalization by $5,857. Assuming 400,000 preventable adverse drug reactions occurred in 2006 in the United States, the total cost of adverse drug reactions for that year was $3.5 billion.[9] Unfortunately, patients admitted to hospitals for reasons other than drug or medication events incur adverse drug reaction-related injuries as well. In hospitalized patients, drug complications were the most common type of adverse event (19%) in a review of disabling injuries caused by medical treatment.[11] Also, a recent study of community hospital patients found an incidence of adverse drug events of 1.1% of hospitalized patients.[12] Tragically, adverse drug reactions are a significant cause of mortality, and may rank as high as fourth among the leading causes of in-hospital death.[12] A meta-analysis of 39 studies revealed the incidence of serious adverse drug reactions at 6.7%, with more than 2 million US patients affected in 1994.[13] Of those patients, 106,000 (0.32%) had fatal adverse drug reactions.

Using these data, we can make some sobering inferences about DDIs. For example, DDIs account for at least 3% to 5% of in-hospital medication errors.[14] Since a 1995 study found that 3% of 264 studied adverse drug events were caused by DDIs and there are 36 million hospital discharges per year in the US, a conservative estimate of the incidence of DDI-linked adverse drug reactions suggests there are at least 110,000 per year in the US that reach the level of detection of harm and are elucidated as true DDIs.[14,15] Since DDIs are often unrecognized, the incidence is surely higher.

Anesthesiologists encounter DDIs in two ways—those they "inherit" due to patients' preexisting medical conditions and medications, and those that are potentially caused in the perioperative period due to several unique aspects of our practice.

As for DDIs that are unwittingly passed on to us from the outpatient prescribers, the data are sobering. For example, a study of retail pharmacies in Norway showed that, for 15% to 20% of patients, commonly prescribed medications that inhibit CYP3A4 and C2D6 were co-prescribed with medications metabolized by those enzymes.[16] Specific DDIs are also associated with identified patient cohorts. For instance, patients with hepatic cirrhosis are known to have a high incidence of potential DDIs (21%), and 13% of these DDIs resulted in harm to the patient (adverse drug reaction). Use of agents with primary hepatic clearance, as well as impaired renal function, increased the risk for adverse drug reactions, and the drugs most commonly associated with DDIs were angiotensin-converting enzyme inhibitors, nonsteroidal anti-inflammatory drugs, diuretics, and anticoagulants. In another study at a US Veterans hospital, researchers identified at least one clinically significant drug interaction in 83% of younger patients and 89% of older patients at an HIV-specialty clinic where most patients have both antiretroviral and nonantiretroviral DDIs.[17] Perhaps predictably, younger patients had more DDIs involving antihistamine, corticosteroid, hormonal, and erectile dysfunction agents, whereas older patients had DDIs involving antihypertensive and antidiabetic agents. Similarly, Miller et al. found that 42% of HIV clinic patients had at least one DDI requiring dosage adjustment, discontinuation of a medication, or both.[18] Independent risk factors for clinically significant DDIs were 1) age older than 42 years; 2) more than three comorbid conditions; 3) more than three antiretroviral agents; and 4) treatment with a protease inhibitor.

There is also abundant evidence of the presence of potential DDIs in inpatient settings of all types. A large review of adverse drug reactions in hospital patients found that 17% were due to DDIs, thus suggesting that the huge number of adverse drug reactions in hospital patients is significantly driven by DDIs.[19] Reimche et al. evaluated all adult admissions to a Canadian teaching hospital and found potential DDIs in 19% of patients, with increased risk ratio for DDIs of approximately 1.5 associated with admission to a medical or surgical service.[20]

A review of DDIs leading to adverse drug reactions in oncology patients, many of whom are also perioperative patients, found that 2% of unplanned admissions were due to DDIs and that one-third of oncology patients had documentary evidence of a potential DDI, with the most likely DDI combinations involving warfarin, antihypertensives, and anticonvulsants.[21] Clearly, these data demonstrate that DDIs are neither uncommon nor insignificant. Even if our personal practices were flawless and we ourselves never undertook any action that resulted in a clinically significant DDI, we would need to exercise continuous vigilance to identify and treat the consequences of the DDIs visited upon us when we undertake the care of referred patients.

How do patients entering the perioperative period incur the risk for potential "new" DDIs? We believe there are four significant factors.

First, drugs and other therapies are stopped and started in the perioperative period. It is pretty easy to understand how this happens. For example, well-meaning primary care providers adjust hypertensive and diabetic medications (both classes of drugs are members of the **Fatal Forty**) when patients go in for preoperative evaluations and "medical optimization." Surgeons prescribe preoperative courses of antibiotics. Analgesic use, both prescription and over-the-counter, increases as patients try to deal with illnesses and injuries. Bowel preps are undertaken. Patients get on the Internet to research dietary and naturopathic strategies to strengthen immune systems, mitigate symptoms, and then start taking herbs and supplements they have read or heard about. Coagulation modifiers such as aspirin, clopidogrel, and warfarin are stopped. Stringent diets of all types are started. And, of course, patterns of smoking, alcohol, and recreational drug use does not stay constant—patients either use less in an attempt to quit before surgery or use more due to anxiety or fear of the upcoming lack of access.

Second, there is acute-on-chronic administration of drugs in the perioperative period. Look for a moment at the Table of Contents of this book. The array of drugs and drug classes we work with every day is truly impressive. Yes, the psychiatrists and the neurologists work with amitriptyline and phenytoin, and the cardiologists work with amiodarone and metoprolol. But these clinicians do not also work with lidocaine, isoflurane, and rocuronium.

Third, there is a veritable "witch's brew" of medications given in the intensive care unit (ICU). ICU physicians practice at a special and rare location on the pharmacological spectrum. The ICU drugs are all potent and most are given intravenously—antibiotics, amiodarone, digoxin, vasopressors, vasodilators, total parenteral nutrition, sedatives, opioids, immunosuppressants, neuromuscular blockers, IV anesthetics, calcium channel blockers, and the list goes on. The potential for DDIs is enormous and will surely trip up the inattentive or unprepared provider. And of course, remember that the debilitated nature of ICU patients almost certainly is an additional risk factor facing providers trying to keep patients safe from the effects of unintended DDIs.

Fourth, the chronic pain practice setting provides many opportunities to encounter and commit DDIs. There is a robust overlap between the chronic pain, addiction, psychiatric, and neurology patient cohorts. The physicians for these very deserving patients utilize a common medication panel that is heavily represented on the **Fatal Forty**—amitriptyline and other tricyclic antidepressants, methadone, buprenorphine, phenytoin, carbamazepine, cyclobenzaprine, phenobarbital, and methadone. Add to this pharmacologic mix ritonavir and smoking tobacco (both members of the ***Fatal Forty***), and it is not surprising that one study found that patients with non cancer chronic pain were found to have a 26% incidence for potential DDIs (in this population, surprisingly, *younger* patients had a slightly higher risk of potential DDIs than those older than 65 years of age, and middle-age patients (35 to 44 years of age) had the highest risk).[22]

How should we begin to identify and deal with perioperative DDIs? The answer is to know our drugs, look for and anticipate the interactions instead of waiting for them to find you, think about potential DDIs in every situation, and above all, ask questions, if you don't know or aren't sure. All practitioners have had the experience of taking care of a patient that doesn't do as well as expected and nobody can figure out why. Keep suspicions and vigilance for DDIs high in your assessments and differential diagnoses.

In the preceding chapters, we have presented our lists of the **Fatal Forty** and **Top Ten**, as well as reading lists for junior and senior anesthesia trainees. We also believe that dedicating time to learning how the core anesthetic drugs are metabolized, and further how each drug acts as a substrate and/or inhibitor, will amply repay the provider's efforts. This is really no different than learning the minimum alveolar concentration (MAC) of each volatile anesthetic or the equipotent dosages of the various opioids—tasks that are set and accepted by all anesthesia trainees and practitioners. To this end, we have created an appendix containing the editors' personal compilations of the enzymes where a number of the most common anesthetic drugs take action. These are the files on our personal desktops—each entry does not necessarily denote a proven or reported DDI, but rather represents the possibility of an interaction that may as yet be unreported or for which the pharmacogenomics are still being elucidated. We have also included below a short list of sources and resources, again from our personal files, which we believe are high in both accuracy and accessibility.

As we have noted elsewhere, we are on the crest of a wave of new information concerning both drug–drug interactions and drug–gene interactions. Of course, the interactions themselves are not new—they have been there all along. But we have now switched on the flashlight. Welcome to the club.

Recommended Sources for the Study of DDIs

Drug Interaction Principles for Medical Practice: Cytochrome P450s, UGTs, P-Glycoproteins. Kelly Cozza MD, Scott Armstrong MD, Jessica Oesterheld MD; American Psychiatric Publishing, Inc. 2003.

Principles of Drug Biotransformation by Evan Kharasch MD PhD in Anesthetic Pharmacology: Physiologic Principles and Clinical Practice. Alex Evers, Mervyn Maze, editors, Churchill Livingstone, 2004.

Drug Interactions Casebook: The Cytochrome P450 System and Beyond. Neil B. Sandson MD; American Psychiatric Publishing Inc. 2003.

Dr. Oesterheld's site is at: **http://www.mhc.com/Cytochromes**

Dr. Flockhart's site is at: **www.drug-interactions.com**

PubMed is at: www.ncbi.nlm.nih.gov/pubmed

The Physicians' Desk Reference online is at: www.pdr.net

Dr. Sandson's website is at: **www.druginteractionworld.com**

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