



Safer Prescribing for Older Adults: Clinical and Business Imperatives Aligned

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For the past 6 years, Dr. B had been treating Mr. J for atrial fibrillation. Two years ago, Dr. B's large multispecialty medical group opened an anticoagulation clinic, and Dr. B referred Mr. J there for ongoing management.

Prior to joining the anticoagulation clinic, roughly 60% of Mr. J's International Normalized Ratio (INR) results had been within the targeted therapeutic range; for the past 2 years, over 90% of his INRs have been therapeutic. Both Dr. B and Mr. J were pleased with the improved results.

Two months ago, the anticoagulation clinic had an unanticipated staffing shortage and had to temporarily refer its patients back to their primary care physicians. Before Mr. J made an appointment, he had a recurrence of his sinusitis and was treated in the multispecialty clinic's urgent care setting with a macrolide antibiotic. The urgent care physician checked Mr. J's INR and told him it was "perfect," but didn't mention the need to follow up due to the potential effect of the macrolide on his anticoagulant.

As usual, Mr. J had his prescription filled at a pharmacy two blocks from his house. His regular pharmacist noticed the potential for a drug interac-

tion, but never mentioned it to the patient and never notified Dr. B. The pharmacist knew that Dr. B was part of a large multispecialty medical group that ran an excellent anticoagulation clinic.

Mr. J called his primary care physician for follow-up on his sinusitis and scheduled an appointment for 2 weeks, but never mentioned the new prescription to the scheduling clerk. Two days before his follow-up appointment, Mr. J was admitted to a local hospital with a massive intracranial hemorrhage. Ten days later, after a stormy hospital course, he died of aspiration pneumonia.

How common are events like this? How could they occur in contemporary society? And, most important, how can we prevent them?

HOW COMMON ARE MEDICATION ERRORS AND ADVERSE DRUG EVENTS?

In 2000, the Institute of Medicine estimated that there were 7000 deaths in the United States each year due to medication error.¹ Adverse drug events (ADEs) account for roughly 95,000 hospital admissions,² 700,000 emergency department visits,² over 3,000,000 office visits,³ and countless unreported symptoms annually (Figure 1). By one recent estimate, the United States spends 30% more money treating the adverse health consequences of medications than on all pharmaceuticals combined.⁴

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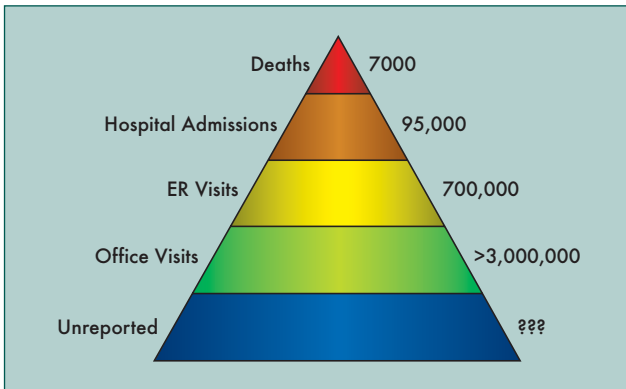


Figure 1. Number of patients impacted by adverse drug events annually.

These are difficult numbers to track. Mr. J was admitted to the Neurology service of his hospital, not the Pharmacologic Toxicity service. Without the ready ability to track these numbers, few groups recognize the true impact of this problem. Even fewer are able to aggressively manage it.

Adverse drug events have been estimated to represent between the 4th and 6th most common cause of death in the United States.⁵ Between 1983 and 1998, annual deaths from acknowledged prescription errors have tripled.⁶ Once driven by hospital-based errors, the balance has shifted to the outpatient arena. In 1983, 75% of deaths from medication errors were generated in the hospital environment. By 1993, the ambulatory setting was responsible for 55% of fatal medication errors.⁷ Clearly, initiatives to improve the safety of medication use must now embrace a focus on ambulatory prescribing.

The medical education process could be more focused on this issue. Less than half of medical schools have clinical rotations that include clinical pharmacology of ADE training in the 3rd or 4th year; of those that do, only 8% consider it mandatory.⁸ Only 16% of Internal Medicine clerkships have formal lectures on adverse drug reactions or drug interactions.⁹ 85% of senior medical students at Thomas Jefferson University chose to not take an

elective in Clinical Pharmacology.¹⁰ The American Medical Association has no training guidelines in this area.

Improving medication safety represents an alignment of clinical, business, and moral imperatives. The good news is that more than 50% of life-threatening or fatal ADEs are likely preventable.¹¹

WHO IS AT THE MOST RISK FOR AN ADE?

Adverse drug events increase dramatically with age. Office visits for ADEs increase from 9% of the population per year at ages 25-44 years to as high as 56.8% between ages 65 and 74 years.¹² There are a number of likely drivers of this pattern:

- 31% of older adults use more than 1 pharmacy, creating challenges for a comprehensive drug review.¹³
- 41% of older adults take at least 5 prescription medications.¹³
- 50% of older adults receive prescriptions from more than 1 prescriber.¹³
- 1 in 12 physician visits for the elderly result in a prescription from the Beers Criteria, a compilation of medications considered to be relatively unsafe for use in older adults.¹⁴ 6,900,000 elderly persons are currently taking a Beers Criteria drug; 1,000,000 are taking a “severe” Beers Criteria drug.¹⁵

Women are also at increased risk of ADEs. Given a similar clinical presentation, women are more than twice as likely as men to receive a Beers Criteria drug.¹⁴ Withdrawn drugs frequently pose greater risk for women, either because of increased sensitivity to the hazards (eg, torsades de pointes) or because the medication’s primary indication is related to a women’s health concern. Between 1997 and 2001, eight out of ten drug withdrawals posed greater risks to women than men.¹⁶

ARE NEW DRUGS SAFER THAN OLD DRUGS?

Goodman and Gilman's The Pharmacological Basis of Therapeutics,¹⁷ the standard textbook of pharmacology for most physicians, advises caution in the use of new medications: "New drugs are inherently more risky because of the relatively small amount of data about their effects."

Elderly persons echo this sense of caution; only 11% of surveyed seniors felt that new drugs were safer than older drugs, and this may be based upon what they have personally witnessed.¹⁸ Over the past ten years, 16 brand-name drugs have been withdrawn for safety reasons. During the past 20 years, two generic drugs have been withdrawn for safety.¹⁹

Half of all new "black box" warnings occur within the first seven years of a drug coming to market; half of drug withdrawals occur within the first two years.²⁰ The emerging patent expirations of sertraline and simvastatin will be 14 years after their release to market. While it is certainly possible to learn important safety concerns about a drug at that point in its life cycle, it is less likely than at an earlier stage.

We will always continue to learn about the benefits and risks of medications after they are released to market. At best, the pivotal studies reviewed by the Food and Drug Administration (FDA) prior to market release are in the range of a few thousand patients. Upon release, many medications ultimately develop market shares of several million patients. Clearly, no matter how well the pre-market studies are designed and implemented, more information

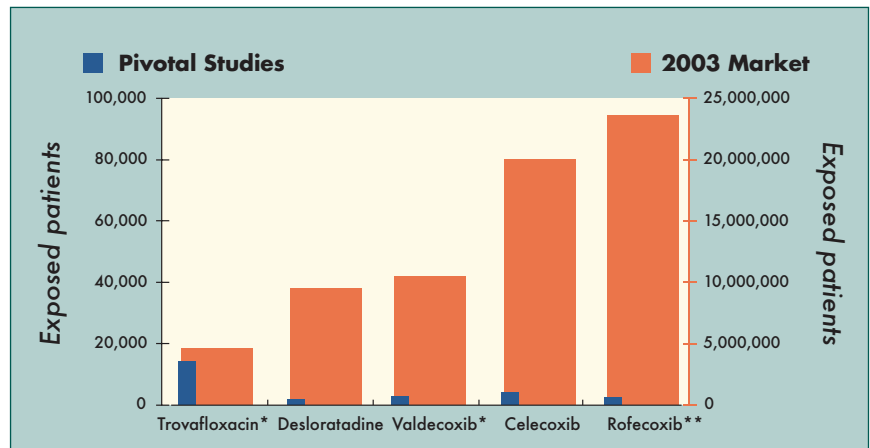


Figure 2. Pivotal studies vs 2003 market size.

* Withdrawn from the U.S. market.

** Withdrawn from the U.S. and worldwide markets.

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will emerge about medications after their release to the market (Figure 2).

Do physicians bear this in mind and prescribe cautiously? A 2003 study asked whether physicians limited the use of cyclooxygenase-2 (COX-2) agents to those situations in which they were believed to have a unique advantage over traditional non-steroidal anti-inflammatory drugs (NSAIDs).²¹ At that point in time, the value proposition of COX-2 agents was that they appeared to have significantly less gastrointestinal complications. The researchers asked two questions: "How often were these drugs prescribed for people with no evidence of risk for a peptic ulcer?" and "How often were these patients also taking aspirin?" (which would erode the theoretic advantages of a COX-2 agent).

The results demonstrated that usage of these new drugs was not limited to those at high risk for NSAID ADEs. Only 35% of COX-2 users had evidence of risk factors for peptic ulcers, and 50% of COX-2 users were also taking aspirin on a regular basis.

Clearly, there is an important role for new medications. However, cautious prescribers should con-

sider limiting the use of new medications to those patients for whom the evidence clearly demonstrates a clinical advantage over older “tried and true” medications.

SYSTEMS TO IMPROVE SAFETY

As is typical of many system failures, the not-so-fictitious scenario at the beginning of this article required a seemingly unlikely combination of events to align. Mr. J slipped through the gaps in multiple imperfect safety systems—the anticoagulation clinic staffing shorting, access to his primary care physician, a treating physician who didn’t recommend a follow-up blood test, a pharmacist who didn’t convey the drug use review (DUR) message, and the patient himself who had been educated about the need to monitor his INR when any new medications were prescribed. In retrospect, the combination of events has a feeling of inevitability. Prospectively, it seems unlikely for so many things to go wrong for the same patient. Reason²² has observed that safety systems are typically imperfect and require redundancy. Nowhere is this better seen than in healthcare today.

FDA letters to physicians

Physician-directed letters have limited effectiveness at changing prescribing behaviors. In October 1997, a few months after troglitazone was released to the market, the FDA identified several cases of liver failure. Four separate letters were mailed to physicians, recommending pretreatment measurement of liver function tests. Testing rose from a baseline level of 9% to a peak of 26% after the 4th letter, and then fell back to 22% shortly before troglitazone was withdrawn from the market in 2000. 10,000,000 prescriptions had been written, and 90 cases of liver fail-

ure were identified. Ultimately, fewer than 5% of patients received all of the recommended liver function testing.^{23,24} Similar patterns have been described with other medications.²⁵

Concurrent electronic drug use review

10.3% of all prescriptions adjudicated in the United States generates an electronic safety alert to the dispensing pharmacist. 88% of those alerts are overridden by the dispensing pharmacist. In roughly equal thirds, pharmacists report that they believed the alert wasn’t important, wasn’t real, or that they already knew about the issue.²⁶

There is emerging evidence that safety messages given directly to the prescriber can alter prescribing patterns. In a closed renal unit, the percentage of safety alerts sent to a prescriber fell by 48% within 3 weeks of implementation of an electronic prescribing system.²⁷ Clearly, the prescribers quickly learned to alter their prescribing choices to avoid the safety alert.

Part of the challenge in DUR today is that it is divorced from the point of prescribing. Pharmacists must disrupt the dispensing process, collect additional clinical information and reach out to the prescriber. There is optimism that electronic prescribing can better integrate the potential value of DUR into clinical care, but the challenge remains to improve the value of DUR messaging. The databases upon which DUR is built today are also in need of improvement.

Adverse drug reaction databases

Today’s databases of adverse drug reactions demonstrate widespread variation. One recent review of four leading drug compendia found that only 2% of drug reactions were identified in all four sources; 72% were listed in any single source.²⁸ A

81% adoption...	Basic	Intermediate	Advanced
Ambulatory visits	136,000	783,000	1,293,000
Total ADEs	218,000	1,252,000	2,068,000
Life-threatening ADEs	14,300	82,620	136,100
Hospitalizations	20,800	115,400	191,100

Figure 3. Projected U.S. annual avoided events.
ADEs = adverse drug events.

status or substance abuse, and it seems to reflect the cyclic increased workload experienced by retail pharmacists during the beginning of the month.³¹ Workload in mail-order pharmacies does not have such a monthly cyclic pattern.³²

Electronic prescribing— The Holy Grail of safety

Illegible physician handwriting has long been recognized as a source of error, but its relative role

similar pattern was found when the analysis was limited to “high-severity” ADEs.²⁹

Reporting ADEs is challenging for physicians; 88% of reports to the FDA come from non-physician sources.³⁰ An improved adverse event reporting system (AERS II) is anticipated by 2008 to transform this to a Web-enabled electronic process, with patient demographics auto-filled from a prescriber’s electronic medical record.

The database of ADEs is in the midst of a major revolution. Starting in October 2005, package inserts are now submitted to the FDA in the form of an interactive electronic database, “Structured Product Labels” (SPLs), instead of the previous non-interactive PDF image. This will create an ability to rapidly disseminate emerging information and integrate with other electronic systems.

Avoid filling a prescription at the beginning of the month

A recent study reviewing 47,000,000 U.S. death certificates from 1979 to 2000 identified a 25% increase in deaths caused by fatal outpatient medication errors the first week of every month. The pattern does not vary with socioeconomic

as compared to other safety opportunities has only recently been articulated. Gandhi et al³³ reviewed four medical practices in the Boston area and found no difference in the rate of preventable ADEs between the two practices that depended upon pen-and-ink prescribing and the two practices that had implemented an electronic prescribing system. The two electronic prescribing practices were using a “basic” system, with little more than the legibility issues addressed. The authors estimated that roughly one-third of the errors could have been prevented with more advanced prescribing systems.

Advanced systems include a variety of functions to support complex decision-making: DUR, allergies, proactive medication recommendations, and preventive monitoring based upon integrated information streams including the International Statistical Classification of Diseases and Related Health Problems (ICD-9) and Current Procedural Terminology (CPT) coding.

The Center for Information Technology Leadership has estimated that such advanced systems could prevent many more ADEs than basic systems³⁴ (Figure 3). Clearly, illegible prescriptions are

an important issue, but it represents only a small fraction of the areas that can be improved with electronic prescribing.

Estimates are that approximately 15% of physicians today have implemented an electronic health record.³⁵ Kleinke³⁶ recently pointed out that given the nonalignment of financial incentives, the question is not why so few physicians have gone this route, but rather why *any* have.

Despite that, progress is clearly being made. Standards are emerging. The Centers for Medicare & Medicaid Services (CMS) has made available VistaRx, the electronic medical record used by the Veterans Affairs clinics. Safe harbors are emerging to facilitate hospital support for medical practice implementation. Performance incentives are being adopted to reward adoption. And ultimately, CMS is accelerating adoption through the Medicare Modernization Act.

KEY LESSONS FOR PRESCRIBING PHYSICIANS

Adverse drug events are more common than is widely appreciated. Some of the patients in your practice are probably experiencing significant clinical side effects today, but you may never know if you don't actively search for them.

Pharmacists receive far more training on pharmacology than do physicians, and remain an incompletely tapped resource in most medical practices. Use their knowledge and skills, especially in the high-risk situations described above.

Newer medications will always carry the baggage of unknown risks; use them only when they have an evidence-based advantage over more proven medications. Establish a practice of defaulting to older medications until the evidence of a clear advantage is persuasive.

Electronic prescribing is worth the effort. Don't stop with simple transcription—evaluate advanced electronic systems.

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