

Toward Safer Prescribing: History, Challenges, and Potential Solutions in Outpatient Medication Safety

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Although the issue of patient safety is not new, it is finally beginning to receive the attention it has long deserved. Unfortunately, as has been demonstrated repeatedly, it usually takes fatal events and negative publicity to precipitate action.

This historical review discusses some milestones that led to the current awareness of the scope of the problem of medication errors and concludes with current and potential strategies to improve safe prescribing for ambulatory patients. Successful approaches for significant improvement will require multiple system enhancements and innovations rather than exhortations for individual prescribers to “try harder.” These solutions include the use of the most recent evolutionary improvement—the Medicare Prescription Drug, Improvement, and Modernization Act of 2003, which has the potential to profoundly enhance the safety of medication usage in ambulatory care.



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laboration with the American Heart Association and the National Pharmacy Association for Surveillance, began the first postmarketing surveillance efforts to publicize ADEs.⁴

- In 1961, thalidomide, which had been prescribed to pregnant women, was discovered to have caused phocomelia (absent or deformed limbs) in 10,000 babies born in western Europe. In 1962, the U.S. Food and Drug Administration (FDA) began postmarketing surveillance for ADEs and subsumed the AMA's process.⁵ The Pharmaceutical Manufacturers Association (PMA), now PhRMA, formed the Commission on Drug Safety.

- In the 1970s, Senator Edward Kennedy led hearings on drug problems, and Ken Melmon, a leading clinical pharmacologist, led the Joint Commission on Prescription Drug Use. There was a growing interest in clinical trial design and methods regarding drug efficacy.
- The 1980s saw growth in spontaneous reports and safety surveillance, starting with 12,000 reports per year at the beginning of the decade and increasing to 250,000 reports by the end of the decade. Drugs recalled around this time included Bendictin® (Merrell Dow), a medication for morning sickness; Phenformin® (Ciba-Geigy) for diabetes; and Zomax® (McNeil), an early nonsteroidal anti-inflammatory drug (NSAID) for arthritis.
- In 1985, the Anesthesiology Patient Safety Foundation began to conduct a thorough re-engineering of the principles of general anesthesia, with a resultant plummeting of intraoperative mortality rates that have yet to be widely replicated elsewhere in medicine. A similar re-engineering of systems for prescribing safety is overdue.
- The 1990s brought to the forefront the potential for drug interactions via cytochrome (CYP) drug-metabolizing enzymes, first presented with erythromycin's effect on terfenadine (e.g., Seldane®, Aventis), resulting in the cardiac arrhythmia torsades de pointes.⁵ Hepatotoxicity and the use of acetaminophen as an over-the-counter medication were also discussed.
- In 1994, Betsy Lehman, a health news reporter for the *Boston Globe*, died of cardiac complications from a four-fold overdose of a chemotherapeutic agent for breast cancer at the Dana Farber Institute. The case caught public attention as evidence that such medical errors can occur even to the best informed of consumers at prestigious institutions.⁷
- The dangerous absence of reliable systems to support the safe delivery of health care finally began to be recog-

EMERGING AWARENESS OF PATIENT SAFETY

Problems relating to medication safety and the avoidance of potential errors have been in the news headlines almost daily, ever since the publication of the Institute of Medicine's 2000 watershed report, *To Err Is Human*.¹ Patient safety improvements have historically followed on the coattails of tragedy, as exemplified by the following events:

- In 1937, the “Elixir of Sulfanilamide” contained the solvent diethylene glycol and killed 105 children. This incident dramatized the need for pre-marketing drug safety, contributing to the congressional amendment of the Federal Food, Drug and Cosmetic Act.²
- Chloramphenicol was isolated and introduced into clinical practice in 1947. By 1950, aplastic anemia (a fatal blood dyscrasia) was identified as an adverse drug event (ADE) resulting from chloramphenicol; this event brought about an increased awareness of the need to report ADEs.³ By 1954, the American Medical Association (AMA), in col-

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nized in the mainstream media in the year 2000 with the release of *To Err Is Human*.¹ Systems supporting safety in outpatient prescribing remain part of a growing field of error-prevention efforts.

- Since 2000, the risk of hypertension associated with phenylpropanolamine (PPA) (e.g., Dexatrim®, Contac®) and the lack of cardioprotective benefits of hormone replacement therapy have been frequently debated.
- The year 2004 saw a cascade of emerging information about the cardiovascular risks and limited gastrointestinal benefits of the cyclooxygenase-2 (COX-2) agents compared with the nonselective NSAIDs. The implications of these events have not yet been fully realized.

SCOPE OF THE PROBLEM

Some authorities estimate that medication errors account for almost 7,000 deaths each year in the U.S.,⁸ others say that adverse drug reactions (ADRs) account for as many as 106,000 deaths annually in the U.S.⁹ From 3% to 28% of all hospital admissions are related to ADRs,¹⁰ and 10% to 20% of ADRs are considered preventable.¹¹

The IOM estimates that medical (not just medication) errors cause 44,000 to 98,000 deaths annually in American hospitals and that medication errors account for one out of 131 outpatient deaths and one out of 854 inpatient deaths.¹²

To put a financial perspective on this problem, the hospital costs of ADRs in the U.S. have been estimated to be as high as \$4 billion per year.¹¹ In total, more than \$175 billion is spent annually in the U.S. to treat ADEs, representing \$1.33 spent treating ADRs for every \$1.00 spent on medications.¹³

In 1980, medical school graduates had to become familiar with the safety profiles of about 60 drugs; by the year 2000, this number had grown to 300 drugs. Potential drug–drug interactions have increased dramatically with the rise in the number of potential drugs administered.¹⁴ Medical schools in the nation now struggle to catch up to ever-growing educational demands, as quoted by one educator:

“The problem that we’re really facing is lack of education. The average medical student receives 27 minutes [of instruction] on opioids in four years of medical school.”¹⁵

Dr. Raymond Woosley, in a personal conversation (June 19, 2004) stated that only about 20 medical schools had formal courses in clinical pharmacology.

In curriculum committees, there is intense pressure for medical students to spend time in required courses as well as a push for them to spend more time taking elective courses. Jefferson Medical College in Philadelphia offers an elective course called Clinical Pharmacology and Therapeutics, but only 30 to 40 of the 230 senior medical students have chosen to take it. A description of the syllabus can be seen on the Thomas Jefferson University Clinical Pharmacology Web site (www.jefferson.edu/clinpharm/academic/acamedstudent.cfm).

SPECIAL CHALLENGES IN AMBULATORY MEDICINE

ADEs are identified more often in ambulatory medicine than in inpatient practices. The evidence suggests that the rate of ADEs among ambulatory patients may be as high as 27% (compared with 3% to 5%, as cited for inpatient therapy), pos-

sibly reflecting the longer rates of exposure or less intensive monitoring for outpatients.¹⁶

ADRs can be difficult to identify and manage in ambulatory care, but the difficulty does not alter the profound importance of this public health problem. The individual events themselves can be subtle and infrequent, lost amid a sea of frenetic outpatient activity. For example, although ADRs are estimated to be the fourth to sixth leading causes of death in the U.S.,¹⁰ NSAIDs are associated with just 5.5 hospital admissions per 10,000 patients treated with these drugs in primary care.¹⁷ Many hospital admissions are not recognized or documented as resulting from an ADR. The challenges in recognizing the problems are exceeded only by their importance in public health.

It is interesting to note that the more severe ADEs are also the most preventable. This may be an unexpected finding, but it is indeed fortunate. In 2003, Gurwitz et al. estimated that more than 25% of 1,900,000 ADEs were potentially avoidable.¹⁸ Furthermore, of 180,000 life-threatening or fatal ADEs per year, more than 50% were considered preventable.¹⁸ These authors concluded that the most severe ADEs were also the most avoidable.

One might think that the largest risk is derived from medications that physicians prescribe infrequently and with which they are not thoroughly familiar. However, most ADEs occur with the drugs that are commonly used; consequently, it is these drugs that should be the prime target of improvement programs. This fact is probably statistically driven: *the more frequently a drug is used, the more errors will result*, even if the percentage of ADEs relative to the number of usages is lower.

In one cohort study of 30,397 Medicare enrollees in a multi-specialty group practice, Gurwitz et al. concluded that “the prescription of a drug for which there was a well-established, clinically important interaction [with warfarin] was a common error.”¹⁸

Another recent study of 49,658 electronic medical records revealed four patterns of care that resulted in 72% of drug-related morbidity events that could have been averted:¹⁹

- prolonged use of NSAIDs in people with known hypertension, congestive heart failure, peptic ulcer disease, or upper gastrointestinal bleeding
- use of angiotensin-converting enzyme (ACE)–inhibitors with inadequate monitoring of serum creatinine and potassium levels
- use of a hypnotic–anxiolytic agent with a long half-life
- failure to provide secondary coronary prophylaxis with beta blockers

These widespread problems result from commonly prescribed medications.

The United States Pharmacopeia (USP) Patient Safety Web site (www.usp.org/patientsafety) offers a wealth of reviews of medication-related issues. Although the site’s MEDMARX medication-reporting program tracks hospitalized patient information (i.e., inpatient medication errors), it is not surprising that *some of the most commonly administered drugs are the ones most often associated with medication errors*.

The five drugs most commonly associated with errors, as

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described in the USP Drug Safety Review of December 8, 2003, were insulin, albuterol, morphine, potassium chloride, and heparin.²⁰

SPECIAL CHALLENGES FOR THE ELDERLY

In 1991, researchers led by Mark Beers at the University of California, Los Angeles, established the first explicit set of criteria for medications that, when used by geriatric nursing-home residents, would be of questionable appropriateness.²¹ Twice updated and independently validated, the Beers List has been documented to correlate with total health care costs, provider costs, facility costs, inpatient hospital days, outpatient visits, and emergency-department visits.²² The largest single risk factor for receiving a Beers List drug is polypharmacy, which is prominent when six or more medications are involved.²³

The Beers List identifies two categories of questionable drugs: (1) those that should be avoided by all elderly patients and (2) those that should be avoided by elderly patients with specific illnesses.

Examples of medications to be avoided regardless of the patient's condition are indomethacin, chlorpropamide, amitriptyline, and long-acting benzodiazepines. Examples of drugs to be avoided by geriatric patients with specific diagnoses include disopyramide for those with congestive heart failure, anticholinergics for those with cognitive impairments, metoclopramide for those with Parkinson's disease, and bupropion for those with seizure disorders.²⁴

Elderly patients in the U.S. receive prescriptions for drugs on the Beers List in one of every 12 physician visits; that is, 16.7 million physician visits annually may include potential prescribing errors. Furthermore, in one recent study, elderly women were twice as likely as men to receive a Beers List drug, especially central nervous system agents and analgesics.²³ This pattern was not explained by the influence of age or the number of prescription drugs in multivariate regression models. Women were more likely to have visits involving antidepressants, anti-anxiety agents, or sedative-hypnotics, but the proportion of visits with analgesic prescriptions were not significantly different for elderly women (18.9%) and men (18.7%) ($P = .79$). For visits in which a pain reliever was prescribed, the women received inappropriate pain medications more often than the men did (10.8% vs. 5.9%; $P < .001$).²³

CURRENT SOLUTIONS TO THE DILEMMA

A variety of systems currently address different aspects of the safety problems. Reason's "Swiss Cheese Model of Defenses" suggests that multiple overlapping solutions are necessary and appropriate, given that no solution is perfect.²⁵

"Dear Doctor Letters" Offer Limited Value

In many cases, pharmaceutical manufacturers first respond to newly identified postmarketing drug interactions by attempting to notify prescribers, anticipating that increased awareness will curtail prescribing for the dangerous combination. Physicians are typically adept at recalling and applying factual knowledge, but ever-increasing demands on their time and memory have contributed to the FDA's recall or voluntary

withdrawal of several medications.²⁶

As an example, the FDA withdrew cisapride (Propulsid®, Janssen), a popular prokinetic gastrointestinal motility agent, in July 2000 after more than 70 fatalities, primarily because of the drug's association with torsades de pointes, which can lead to ventricular fibrillation and death. The problem typically occurred after cisapride was taken concurrently with another medication, a metabolic inhibitor, which was known to increase the risk of this reaction. Of the interacting medication pairs, 50% were prescribed by the same physicians, 89% were dispensed by the same pharmacies, and 17% were dispensed on the same day.²⁷

Before withdrawing cisapride from the market, the manufacturer, in concert with the FDA, made four label changes and issued a number of "Dear Doctor" letters. Although some prescribing physicians responded immediately, no sustained change in the prescribing pattern for cisapride was observed as a result of these interventions.²⁷

Electronic Drug Use Review Supports Prescribing

Today, about 10% of all prescriptions filled in the U.S. trigger a concurrent safety alert to be sent to the dispensing pharmacist. Of these alerts, 88% are simply overridden by the pharmacist. In roughly one third of the cases, pharmacists were already aware of the problem; for another third, they did not believe that the problem existed; and in another third, they thought that the problem was insignificant.²⁸

This high volume of alerts in the absence of action diffuses the value of the more significant messages, contributing to "signal overload" by dispensing pharmacists. This problem is beginning to be addressed by several of the new and recent initiatives described later (see "Emerging Solutions").

Retrospective drug use review (rDUR) systems typically involve written communications to the prescriber after the prescription has been dispensed. Given the lag time between prescribing, dispensing, and receipt of this information, rDUR systems are typically used to address patterns of care or subacute concerns that require long term follow-up.

In an unpublished survey by Express Scripts of 471 prescribers who received rDUR letters, 60% found them useful, 25% were ambivalent, and only 15% did not find them useful. Thirty-eight percent of surveyed physicians reported changing treatment plans after receiving the rDUR intervention. A six-month pre-rDUR and post-rDUR intervention claims analysis demonstrated up to a 22% decrease in prescribing selected drug categories compared with randomized control groups without rDUR.

Critical Database Selection Is Required for Checking Electronic Drug Interactions

There is little agreement as to which drug-drug interactions (DDIs) are the most clinically important. Abarca reviewed five leading drug compendia and discovered that most DDIs were identified in only one or two of these sources and were absent from the others.²⁹ Of 2,372 interactions listed in at least one of the five sources, only 65 were listed in all five sources. More recently, the same researcher and his colleagues surveyed the "high-severity" DDIs listed in four leading DDI compendia. There was very poor concordance in the listings

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between compendia; nearly three-fourths of the DDIs were found in only one or another of the compendia. Only 2% of the DDIs were identified in all four compendia.³⁰

Cavuto et al. reported the results of presenting paired prescriptions for terfenadine and ketoconazole, a combination that has been established as presenting an increased risk of torsades de pointes.³¹ These paired prescriptions were presented simultaneously to 50 pharmacies in the Washington, DC, area and to seven more pharmacies across the U.S. Both prescriptions were filled 35% of the time despite electronic drug-interaction software. Either the software programs did not identify the drug interaction, or the pharmacists chose to dispense the medications even though they had received an alert.³¹

Hazlet et al. presented 16 well-documented DDIs in six fictitious patients to 516 community pharmacies in Washington State, representing nine different DDI software programs.³² The software was unable to detect 35% of these DDIs. More surprising than the variation among software vendors was the variation within given programs—this can be attributed to inconsistent software installation and operations at different locations.

Electronic Prescribing Shows Promise

Ghandi et al. reviewed four medical practices in Boston, two with traditional pen-and-paper prescriptions and two with basic e-prescribing.¹⁶ The investigators were unable to identify a significant difference in the rates of preventable ADEs between these two models. They speculated that part of the lack of difference was related to the non-advanced nature of e-prescribing in the groups that they studied, and they concluded that advanced systems could have avoided seven of the 20 preventable events.

The IOM recommends that health care organizations implement proven medication-safety processes, including computerized physician order entry (CPOE), to decrease medication errors and to improve health care in America.¹ Evidence supporting the improved safety of advanced e-prescribing is beginning to take shape. A study in 2004 showed a 50% drop in paired alerts sent to prescribers in a renal unit after three weeks of exposure to the alerts, suggesting that sending the warnings directly to the physician contributed to their learning safer prescribing patterns.³³

According to David Bates, MD, who chairs the USP CPOE project team, computerized systems have great potential to improve practitioner prescribing, although functionality and design decisions will have a significant effect on the ability of the system to prevent prescribing errors. In his experience, the use of CPOE has decreased the incidence of serious medication errors by 55%. Each preventable ADE costs approximately \$6,000.³⁴ Currently, 62% of hospitals plan to implement CPOE in their facilities,³⁵ and at the beginning of 2005, 23% of primary care physicians expected to purchase an electronic health record within the next 12 months.³⁶

More than a dozen CPOE vendor products are on the market; eight are already being used in hospitals beyond the pilot stage. Six of the most popular products are marketed by the following firms: Cerner, CliniComp, Eclipsys, Autros, Epic, and McKesson. The Leapfrog Group has developed a set of standards for CPOE to try to unify and standardize these systems.

The basic data for these systems, as well as for four layers of decision support, have been described in a White Paper from the USP.³⁴

E-prescribing has the potential to be coupled with intelligent decision support.³⁷ Ideally, this technology would incorporate sophisticated data streams and enhance prescribing by providing patient-specific, prioritized, comprehensive, evidence-based clinical knowledge of monitoring at the moment the prescription is written. It has been projected that advanced e-prescribing will prevent 76% of avoidable errors annually; this figure represents 2,068,000 ADEs (136,100 of which would be life-threatening) and 191,000 hospitalizations. The promise of this technological advancement has yet to be realized or well documented.³⁷

EMERGING SOLUTIONS

Four potential solutions to the patient medication-safety dilemma are described here:

1. The Academy of Managed Care Pharmacy has developed and published *Guiding Principles for Effective Electronic Messaging* (www.amcp.org). As these principles become more widely adopted, they should significantly increase the value of safety alerts to pharmacists. Such standardized messages will be clearer, more action-focused, and less redundant than current alerts.³⁸ These same enhancements will also benefit physicians who prescribe electronically.
2. The USP, among its many vital services, has formed a Therapeutic Decision Making Expert Committee to identify those drug-drug interactions for which the risk of harm is the greatest. The USP is evaluating the level of evidence connecting specific drug alerts with an eventual impact on health outcome. At the end of this process, the USP plans to issue recommendations regarding the appropriateness of including or excluding specific drug-drug interactions in a drug review safety program.³⁹
3. Senior Outpatient Safety (“SOS Rx”), a broad collaborative coalition, has been convened by the National Consumer’s League under an unrestricted grant from Express Scripts.⁴⁰ Representing consumers, caregivers, government agencies, retailers, health plans, pharmacy benefit managers, manufacturers, and professional societies, this group is focusing on advocacy for e-prescribing, personal medication records, education of high-risk patients, and the development of a clearinghouse of information about best practices for high-risk situations.
4. The Medicare Modernization Act of 2003 has introduced a number of initiatives for improving patient safety:
 - Pharmacy transactions will have to include both concurrent and retrospective DURs with associated safety interventions.
 - The adoption of e-prescribing will be accelerated.
 - An intervention called Medication Therapy Management Services will be implemented to improve self-management of complex medication regimens and to aid in detecting ADRs.

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CONCLUSION

The field of safe prescribing in ambulatory medicine is emerging as a focus of study, with much work yet to be done. As with many opportunities for improvement, the answers can best be found in *systems development* rather than in blaming individuals for human error.

This review has shown that past tragedies can draw attention to problems and possible solutions. Sorting through these potential solutions and debugging new systems will require dedication and persistence. An array of business entities with new products and services, consumer advocacy, and professional organizations is actively promoting this important agenda.

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