

Medication Safety

Moving From Illusion to Reality

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The importance of medication safety has been recognized for many years, but only recently has it reemerged as a major public health issue based on numerous recent studies and high-profile safety events.¹ Drug safety dates back to the 1950s, when in response to reports of chloramphenicol-associated aplastic anemia, the American Medical Association established an adverse drug reaction (ADR) reporting system and the Food and Drug Administration began requiring pharmaceutical manufacturers to report ADRs.¹ This effort to detect heretofore unknown, serious adverse effects of medications in postmarket use relied on voluntary reporting, which also became common practice in most health care organizations.

In the 1960s, Jick and colleagues² began to focus on the safety of drugs in everyday practice, using a concurrent study approach instead of voluntary reporting. The authors found that 30% of the medical inpatients in their study experienced at least 1 ADR during their hospital stay, and 3% of hospitalizations were directly attributable to ADRs. They also estimated that 29 000 deaths due to ADRs occurred annually in the United States.² However, adverse effects of drugs were viewed as an unavoidable part of modern medical therapy; in a later publication, Jick noted that "the rates and severity of adverse reactions to individual drugs are remarkably low in view of their pharmacological properties."³

Now, 30 years later, with more sophisticated and comprehensive means to detect adverse drug events (ADEs), studies^{1, 4-6} reveal that ADEs occur in 6.5% to more than 20% of hospitalized patients, and that many of these ADEs are avoidable. Tolerance for the illusion that medication safety is as good as it can be has finally begun to change.⁷

In this issue of THE JOURNAL, Gurwitz and colleagues⁸ report findings from an important new study of medication safety in the outpatient setting among Medicare patients (most of whom were enrolled in a Medicare health maintenance organization plan [Medicare + Choice Plan]). This study builds on a previous study of this group in the inpatient and nursing home settings in which they developed and tested consistent methods for the detection, characterization, and analysis of ADEs.⁹ Despite the new setting, the current study confirms many previous observations about medication safety and error,^{4, 9} but with several important new findings. Adverse drug events occurred at a rate of 50.1 per 1000 person-years, of which 13.8 per 1000 person-years were preventable. This study indicates that the most frequent classes of drugs associated with ADEs were cardiovascular agents, antibiotics, diuretics, nonopioid analgesics, and anticoagulants. These rates largely reflect their prevalence of use with the exception of anticoagulants, which were associated with a disproportionately high rate of ADEs.

As previous studies have shown,^{4, 9} prescribing medications and appropriate monitoring of drug therapy remain significant and provide largely unmet opportunities for improvement. Of note, lack of patient adherence, known to be associated with therapeutic failure,¹⁰ also was found to pose a safety risk.

Extrapolating the rate of ADEs from the study by Gurwitz et al⁸ to the total Medicare population, it was estimated that as many as 1 900 000 ADEs may occur annually and perhaps as many as 180 000 of these ADEs are life-threatening or fatal. However, as the authors acknowledge, this estimate may be conservative as several factors in their study design, including incomplete review of clinic notes and no information collected from patients, may have led to underdetection of ADEs. Obtaining an accurate measure of the scope of the problem of ADEs is a first step in addressing the problem.

Most current efforts in this area use retrospective chart review to detect ADEs. The significant limitations of this approach are widely acknowledged, yet a relentless debate about this method continues.¹¹⁻¹² Far

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more attention should be focused on the critical need to develop new methods to improve the detection of ADEs and other adverse events (AEs), especially in outpatient settings where minimal tracking of these events occurs.⁸ Numerous new methods for detecting ADEs, including both electronic¹³ and chart-based approaches,^{6, 14} are currently being developed, tested, and implemented for both inpatient and outpatient settings, and several were used in the study by Gurwitz et al.⁸ Electronic approaches include searching for triggers such as abnormal laboratory test results and pharmacy information, the administration of known antidotes, the use of diagnostic codes and structured documentation possibly related to ADEs, and the use of free-text searching of text-based clinic notes focusing on key words or terms or using complex algorithms (natural language processing). The Institute for Healthcare Improvement through its collaboration has modified an electronic trigger tool to improve the detection of ADEs⁵ into a chart-based tool that has been used to improve the detection of ADEs and many other types of AEs in diverse settings, such as general hospital wards, intensive care units, emergency departments, and outpatient clinics.^{6, 14}

Other challenges in measuring the scope of ADEs include defining and assessing preventability. Gurwitz et al.⁸ found that 28% of ADEs were preventable, with 42% of serious, life-threatening, or fatal ADEs deemed preventable vs 18.7% of those considered significant (least serious). Other studies have shown a wide range of preventability from 13% to 70% of ADEs.^{1, 15} In the current study, rashes and diarrhea related to antibiotic use were considered not preventable. With advances in pharmacogenomics, antibiotic therapy might be tailored to individual patient risks and ADEs could be avoided.¹⁶ Furthermore, if overuse of antibiotics were addressed, many ADEs caused by antibiotics might be prevented.

These issues defining preventability highlight the limitations of the concept of preventability, which is primarily rooted in medication misuse and does not adequately address medication overuse (eg, antibiotics) or the underuse of beneficial drug therapies (such as cholesterol-lowering agents), which represent a much larger safety problem, particularly in elderly patients.¹⁷ In most studies of AEs, reviewer agreement on occurrence and preventability is highly dependent on reviewer perspective, consensus, and level of confidence.^{12, 18} Rigid, subjective, and static definitions of preventability may not only reduce potential opportunities for improvement but also may seriously hamper efforts to improve the detection and reporting of all AEs. For example, if the detection and reporting of nosocomial infections were limited to only those infections that were definitely preventable or clearly related to error, far fewer infections would be detected and reported. The Joint Commission on Accreditation of Healthcare Organizations has recently observed this phenomenon with respect to nosocomial infections in its Sentinel Event Program.¹⁹

Interventions to reduce ADEs need to be implemented. Several interventions have been demonstrated to improve ambulatory drug use in older persons, including curbing overuse of medications by identifying inappropriate medications and stopping their use²⁰ and addressing underuse of beneficial medications.²¹ Patient nonadherence may be remedied through patient education, but commonly used approaches to ensure patient adherence often are not effective,¹⁰ and novel new methods to involve patients more directly in all aspects of their care are needed. In addition, several interventions effective at reducing medication errors in the inpatient setting could be generalized to the outpatient setting. These include computerized physician order entry of medications with decision support (ie, drug interaction checking, allergy checking, dose and frequency adjusting, and treatment duration limits), clinical pharmacist consultation services, and clinics for anticoagulation therapy.²²⁻²⁴

While appropriate prescribing and monitoring is undoubtedly appropriate to measure process improvement, most interventions have not yet been shown to reduce ADEs.^{1, 22-24} This finding is not unexpected because measuring medication errors is easier than measuring ADEs, especially if those medication errors are voluntarily reported.^{5, 25} In addition, most medication errors do not result in ADEs.¹ Regardless of the difficulty in measuring a clear impact of best practices for patient safety on lives saved or injuries prevented, the lack of evidence has delayed implementation of these systems in hospital and practice settings.²² Addressing this lack of evidence will be difficult, given the methodological challenges of conducting rigorous trials of process-based best practices for patient safety and the inherent lack of funding to conduct these kinds of scientific trials.²² However, proof that best practices for patient safety prevent AEs, avoid injuries, or save lives will be essential to convince skeptics that these practices should be broadly implemented.

Establishing the best evidence for the effectiveness of patient safety practices will not be sufficient to spur widespread adoption of such practices. Patient safety is viewed among many health care stakeholders as another unfunded mandate. Many organizations have expressed skepticism associated with patient safety initiatives about the true cost savings and who actually benefits.²⁶ To address this skepticism, programs, such as the Leapfrog Group Initiative,²⁷ are using financial incentives to encourage better performance in safety and quality of care. The Leapfrog Group has developed 3 patient safety standards that reward publicly transparent hospital performance. A forthcoming Leapfrog standard will encompass ambulatory electronic prescribing of medications with decision support and electronic laboratory results review (Arnold Milstein, MD, written communication, February 3, 2002). Incentives also are needed to improve the detection and reporting of AEs. One approach would be to require documentation and reporting of specific types of AEs as a part of higher reimbursement for a diagnosis related group, which could have a dramatic

impact on the underdetection and underreporting of AEs.

Patient safety efforts also require additional conceptual models. Aviation has provided valuable insights, but its applicability to health care is clearly limited. Infection control is a model that bears close scrutiny. This successful model arose in the 1960s from conditions not dissimilar to patient safety today (nosocomial infections abruptly became the province of public health officers with the massive nationwide epidemic of hospital staphylococcal infections in 1957-1958) and it has successfully overcome many barriers faced by patient safety.²⁹⁻³⁰ These barriers include measuring the overall extent of the problem; the need for common definitions, terminologies, and classification approaches; the limitations of voluntary reporting and the need for surveillance programs; the creation of national benchmarking systems (National Nosocomial Infection Survey); the need for a scientific approach to investigation (epidemiological rather than root-cause analysis for every nosocomial infection) to guide the appropriate level of case aggregation for investigation and analysis; the need for a nonregulatory body to help investigate epidemics (AEs); and the need for a rigorous scientific basis to evaluate potential interventions. Beyond these immediate barriers, patient safety will ultimately need to be part of a larger fix of the broken health care system, not a stand-alone property. Future potential priorities in patient safety within this larger milieu can be found in 2 new publications from the Institute of Medicine.³¹⁻³²

The study by Gurwitz et al⁸ has helped to provide a clearer view of the illusion of medication safety this time in the outpatient arena. When their work is combined with other studies,^{1, 4-6,9} medications still pose a significant risk to patients across the continuum of care despite decades of research and advances in drug therapy. Although the potential exists to reduce this risk markedly with existing interventions, lack of progress in this area is compounded by the increasing complexity of drug therapies and the increasing vulnerability of those who receive them. It is time to move beyond the illusion of medication safety to face the difficult reality of acknowledging the significant risk that medications pose to patients and implementing strategies to reduce it.

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REFERENCES

1. Kilbridge P, Classen D. Surveillance for adverse drug events: history, methods and current issues. VHA. Irving, Tex: VHA Inc; 2002. Research Series.
2. Jick H, Miettinen OS, Shapiro S, Lewis GP, Siskind V, Slone D. Comprehensive drug surveillance. *JAMA*. 1970;213:1455-1460. [CrossRef](#) | [MEDLINE](#)
3. Jick H. Drugs—remarkably nontoxic. *N Engl J Med*. 1974;291:824-828. [ISI](#) | [MEDLINE](#)
4. Bates DW, Cullen DJ, Laird N, et al. Incidence of adverse drug events and potential adverse drug events: implications for prevention. *JAMA*. 1995;274:29-34. [ABSTRACT](#)
5. Classen DC, Pestotnik SL, Evans RS, Burke JR. Computerized surveillance of adverse drug events in hospital patients. *JAMA*. 1991;266:2847-2851. [ABSTRACT](#)
6. Rozich JD, Haraden CR, Resar RK. The adverse drug event trigger tool: a practical methodology for measuring medication-related harm. *Qual Saf Health Care*. In press.
7. Institute of Medicine, Committee on Quality of Health Care in America. *To Err Is Human: Building a Safer Health System*. Washington, DC: National Academy Press; 1999.
8. Gurwitz JH, Field TS, Harrold LR, et al. Incidence and preventability of adverse drug events among older persons in the ambulatory setting. *JAMA*. 2003;289:1107-1116. [ABSTRACT/FULL TEXT](#)
9. Gurwitz JH, Field TS, Avorn J, et al. Incidence and preventability of adverse drug events in nursing homes. *Am J Med*. 2000;109:87-94. [CrossRef](#) | [ISI](#) | [MEDLINE](#)
10. McDonald HP, Garg AX, Haynes RB. Interventions to enhance patient adherence to medication prescriptions: scientific review. *JAMA*. 2002;288:2868-2879. [ABSTRACT/FULL TEXT](#)
11. McDonald CJ, Weiner M, Hui SL. Deaths due to medical errors are exaggerated in Institute of Medicine report. *JAMA*. 2000;284:93-95. [FULL TEXT](#)

12. Hayward RA, Hofer TP. Estimating hospital deaths due to medical errors: preventability is in the eye of the reviewer. *JAMA*. 2001;286:415-420. [ABSTRACT/FULL TEXT](#)
13. Bates DW, Evans RS, Murff H, Stetson PD, Pizziferri L, Hripcsak G. Detecting adverse events using information technology. *J Am Med Inform Assoc*. Available as a preprint: <http://www.jamia.org/cgi/content/abstract/m1074v1>. Accessibility verified February 17, 2003.
14. Resar RK, Rozich JD, Classen DC. Innovative strategies to improve health care: methodology and rationale for the measurement of harm with trigger tools. *Qual Saf Health Care*. In press.
15. Classen DC. Adverse drug events and medication errors: the scientific perspective. In Scheffler AL, Zipperer LA, eds. *Proceedings of Enhancing Patient Safety and Reducing Errors in Health Care*. Chicago, Ill: National Patient Safety Foundation; 1999.
16. Phillips KA, Veenstra DL, Oren E, Lee JK, Sadee W. Potential role of pharmacogenomics in reducing adverse drug reactions: a systematic review. *JAMA*. 2001;286:2270-2279. [ABSTRACT/FULL TEXT](#)
17. Avorn J. Improving drug use in elderly patients: getting to the next level. *JAMA*. 2001;286:2866-2868. [FULL TEXT](#)
18. Thomas EJ, Lipsitz SR, Studdert DM, Brennan TA. The reliability of medical record review for estimating adverse event rates. *Ann Intern Med*. 2002;136:812-816. [ISI](#) | [MEDLINE](#)
19. Joint Commission on Accreditation of Healthcare Organizations Web site. Infection control related sentinel events. JCAHO Sentinel Event Alert Issue 28, January 28, 2003. Available at: http://www.jcaho.org/about + us/news + letters/sentinel + event + alert/sea_28.htm. Accessed February 12, 2003.
20. Beers MH. Explicit criteria for determining potentially inappropriate medication use in the elderly: an update. *Arch Intern Med*. 1997;157:1531-1536. [ABSTRACT](#)
21. Wenger NS, Shekelle P, Davidoff F, Mulrow C. Quality indicators for assessing care of vulnerable elders. *Ann Intern Med*. 2001;135:641-758. [ISI](#) | [MEDLINE](#)
22. Leape LL, Berwick DM, Bates DW. What practices will most improve patient safety? evidence-based medicine meets patient safety. *JAMA*. 2002;288:501-507. [FULL TEXT](#)
23. Evans RS, Pestotnik SL, Classen DC, et al. A computer-assisted management program for antibiotics and other antiinfective agents. *N Engl J Med*. 1998;338:232-238. [ABSTRACT/FULL TEXT](#)
24. Chiquette E, Amato MG, Bussey HI. Comparison of an anticoagulation clinic with usual medical care: anticoagulation control, patient outcomes, and health care costs. *Arch Intern Med*. 1998;158:1641-1647. [ABSTRACT/FULL TEXT](#)
25. Cullen DJ, Bates DW, Small SD, Cooper JB, Nemeskal AR, Leape LL. The incident reporting system does not detect adverse drug events: a problem for quality improvement. *Jt Comm J Qual Improv*. 1995;21:541-548. [MEDLINE](#)
26. Weeks WP, Bagian JP. Making the business case for patient safety. *Jt Comm J Qual Improv*. 2003;29:51-54. [MEDLINE](#)
27. Milstein A, Galvin RS, Delbanco SF, Salber P, Buck CR Jr. Improving the safety of health care: the leapfrog initiative. *Eff Clin Pract*. 2000;3:313-316. [MEDLINE](#)
28. Wilke MH, Schenker M, Hoffmann G. Detection and documentation of DRG-relevant comorbidities using laboratory tests. *Aust Health Rev*. 2002;25:152-160. [MEDLINE](#)
29. Gerberding JL. Hospital-onset infections: a patient safety issue. *Ann Intern Med*. 2002;137:665-670. [ISI](#) | [MEDLINE](#)
30. Burke JP. Infection control—a problem for patient safety. *N Engl J Med*. 2003;348:651-656. [FULL TEXT](#)
31. Institute of Medicine, Committee on Identifying Priorities Areas for Quality Improvement. *Priority Areas for National Action: Transforming Health Care Quality*. Washington, DC: National Academy Press; 2003.
32. Institute of Medicine, Committee on Rapid Advance Demonstration Projects. *Fostering Advances in Health Care: Learning From System Demonstrations*. Washington, DC: National Academy Press; 2002.

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