United States General Accounting Office

GAO

Report to Congressional Requesters

January 2000

ADVERSE DRUG EVENTS

The Magnitude of Health Risk Is Uncertain Because of Limited Incidence Data

GAO/HEHS-00-21

GAO

United States
General Accounting Office
Washington, D.C. 20548

Health, Education, and
Human Services Division

B-281822

January 18, 2000

Congressional Requesters

In 1998, about 2.7 billion prescriptions were filled in the United States. Prescription drugs have great clinical benefits, but they also have risks. Although most health problems associated with the use of pharmaceuticals are relatively minor, serious adverse drug events (ADE) that lead to hospitalization, disability, or death do occur. Because exposure to prescription drugs is so high, even a very low ADE rate can lead to a large number of serious injuries and deaths. The Food and Drug Administration (FDA), the federal agency that approves drugs for marketing; the pharmaceutical industry; physician groups; consumer advocates; and health care researchers all agree that every medicine has risks as well as benefits. However, they disagree substantially about the extent of the risk, how to categorize ADEs, and what, if anything, should be done to reduce their number.

In light of this debate, you asked us to summarize from available research what is known about ADEs. In this report, we (1) describe the different types and causes of ADEs, (2) examine the evidence on the overall incidence and cost of ADEs in the United States, and (3) describe measures that have been proposed to reduce the number and severity of ADEs. To conduct our work, we reviewed the relevant scientific literature published since 1980, organized a symposium of experts, and spoke with experts in government, academia, and industry. Our methodology is described in appendix I. We conducted our work between November 1998 and December 1999 in accordance with generally accepted government auditing standards. At your request, we plan to examine next the adequacy of the U.S. system for monitoring the safety of prescription drugs that FDA has approved for marketing.

Results in Brief

Adverse drug events arise either from adverse drug reactions (ADR), which are previously known or newly detected side effects of drugs, or from medication errors committed by health care professionals or the patients themselves. Many types of drugs can cause ADRs; the drugs reported as associated with ADRs vary among different studies, depending on the patients and settings examined. Two factors that can increase the risk of a patient's suffering from an ADR are illness severity and intensity of treatment, including taking several drugs simultaneously. Studies of several hospital populations found that most medication errors did not

cause ADEs, but because so many drug doses were given, an estimated quarter to half of all ADEs among the hospital patients resulted from medication errors. Other studies found that medication errors were most often the result of physicians' prescribing errors and nurses' errors in administering drugs. Certain classes of drugs have consistently been associated with medication errors, including analgesics, antibiotics, psychotropics, and cardiovascular drugs.

Although it is clear that a wide range of commonly used drugs cause ADEs with potentially serious consequences for patients, relatively little is known about their frequency. Data routinely collected on ADEs during clinical trials or after drugs are marketed are intended to identify the ADEs that are associated with particular drugs and do not focus on their frequency. Information on the overall incidence of ADEs from all drugs is limited to a few research studies that typically examined the experience of patients in one or two specific institutions—generally hospitals or sometimes nursing homes—leaving the overall incidence of ADEs in outpatient care largely unexplored. The most broadly based information on ADE incidence comes from two studies drawing on statewide samples of hospital patients. These studies applied a particularly restrictive definition of ADE in finding that ADEs occurred at a rate of 0.56 for every 100 patients admitted in Colorado and Utah, 0.72 in New York. Other studies that used broader definitions found a range of 2 to 30 ADEs per 100 hospital admissions. Two studies of ADEs in individual nursing homes reported an incidence of 0.44 to 0.71 ADEs per patient month. Although studies have estimated the overall rate of fatalities from ADEs and the total costs of treating ADEs, their estimates are open to question because of the limited underlying data on overall incidence available to support them.

Greater understanding of certain factors that affect the likelihood of ADEs has led researchers and patient safety advocates to suggest a range of measures to decrease their number and severity. Proposals for reducing ADRs include improving communication between patients and physicians about the risks and benefits of medications and expanding and accelerating research on the safety of marketed drugs to more quickly detect previously unknown ADRs and determine the risk factors that increase their likelihood. Suggestions for reducing medication errors include developing computerized prescribing and dispensing systems to detect possible errors, avoiding confusing names and packaging for medications, increasing the role of pharmacists as advisers to physicians prescribing drugs and in monitoring drug therapy, and improving health care providers' pharmaceutical education.

Background

Each year, nearly half of all Americans take prescription drugs, spending about $100 billion. For many medical conditions, pharmaceuticals are the treatment of choice. Pharmaceuticals have contributed to lengthening life expectancy by virtually eliminating the risk from some formerly deadly infectious diseases and, more recently, by providing tools for more effective management of chronic conditions such as heart disease, hypertension, diabetes, and asthma.

Like all medical interventions, pharmaceuticals have risks as well as benefits. Serious ADEs—those that cause hospitalization, significant disability, or death—are relatively rare. Most ADEs involve transient and less severe side effects from drugs, such as nausea or rash. Many ADEs reflect the inherent risks, both known and unknown, of drugs that are prescribed and administered correctly; these are what we call ADRs in this report. Other ADEs stem from errors in prescribing, dispensing, or administering prescription drugs. Common examples include physicians' prescribing antibiotics to patients who have documented allergies to them, nurses' not properly diluting intravenous solutions, and patients' failing to take medications as directed.[1]

FDA within the Department of Health and Human Services decides which drugs are approved for use by the general public. It assesses the information that pharmaceutical companies provide when they seek approval to market a drug to determine whether the drug is both safe and effective in treating one or more specified medical conditions. In making this assessment, FDA considers safety not in absolute terms but as a balance of risks and benefits. For example, a new drug may have serious adverse effects on some patients but still win FDA's approval because of its overall effectiveness in treating certain conditions relative to alternative therapies. FDA also considers drugs in relation to the illness they are meant to cure or relieve. Patients with life-threatening conditions may be willing to assume more risk than other patients.

FDA continues to assess the risks and benefits of drugs after they are initially approved, primarily on the basis of reports health professionals and patients make about their experience with them. These reports are voluntarily submitted to either FDA itself or, more commonly, a drug's manufacturer, which is required to pass them on to FDA. As FDA and the medical community learn more about a particular drug, FDA may require

[1]The distinction between medication errors and an ADE associated with the inherent risks of drugs is sometimes ambiguous. For example, some drugs are difficult to use safely because toxic doses are only slightly larger than those required for treatment, or appropriate dosing levels may vary over time, requiring frequent adjustments. These factors provide abundant opportunities for medication errors.

manufacturers to change its labeling. Such changes may restrict the conditions for which the drug is approved or require certain safety precautions. However, new information can also point to expanded uses for a drug. For example, it was recently discovered that the diuretic spironolactone, which has been marketed for 30 years, may substantially reduce the risk of death in patients with congestive heart failure (Pitt, 1999).[2] In other cases, new applications of a drug have revealed previously unsuspected risks. After more than 20 years on the market, the drug fenfluramine was linked to damaged heart valves when used in combination with phentermine, another weight-loss medication. This was one of the rare instances in which FDA requested that the manufacturer withdraw its drug from the market rather than change the label.

The Risk of ADEs Has Multiple Factors

Some ADRs are the predictable result of a drug's known pharmacological properties, some become predictable as experience with using a drug expands, and others are not predictable because they are caused by individual sensitivities or allergies in particular patients. Many types of drugs cause ADRs: Different studies vary in the drugs they report as associated with ADRs, depending on the patients and settings they examine. Two clinical factors known to increase the risk of a patient's suffering an ADR are the severity of illness and intensity of treatment, including taking several drugs simultaneously (polypharmacy). Several studies of hospital patients found that most medication errors did not cause an ADE but that the few that did were still so numerous that they accounted for a quarter to half of all ADEs. Other studies found that medication errors were most often the result of physicians' prescribing errors and nurses' administration errors. Analgesics, antibiotics, psychotropics, and cardiovascular drugs are among the drug classes that have been consistently associated with a greater proportion of medication errors.

Inherent Properties of Medications Lead to Many ADEs

Many ADRs are the predictable result of a drug's known pharmacological properties and are often listed in a medication's label. For example, hemorrhaging is the most common ADR for warfarin, a drug that reduces the risk of heart attack, stroke, and other conditions by decreasing the clotting ability of blood. Nonsteroidal anti-inflammatory drugs (NSAID), prescribed over long periods for rheumatoid arthritis, suppress enzymes that protect the lining of the stomach and intestines, which causes serious gastrointestinal complications in a small percentage of patients.

[2]Interlinear bibliographic citations refer to the bibliography at the end of this report.

Other ADRs, including allergic reactions, are unpredictable, caused by sensitivities in particular patients who have neither a known risk factor nor a history of adverse reactions to a specific drug. An unpredictable ADR is more likely to cause disability or death than one that is predictable. Still other ADRs are related to previously undetected inherent risks, including drug-drug and drug-food interactions, that become evident as a drug is used by many types of patients, having many kinds of comorbidities and taking many other medications, including over-the-counter drugs and dietary supplements. FDA's system for collecting voluntary reports on adverse experiences with marketed drugs is designed specifically to uncover these kinds of previously unknown risks.

Many types of drugs can cause ADRs. Therefore, the drugs associated with ADRs in particular studies vary, depending on the patients and clinical settings studied. In addition, some drug classes are associated with a substantial number of ADRs simply because they are prescribed to many patients. These include antibiotics, narcotic analgesics, drugs to control hyperglycemia in type II diabetics, psychotropic drugs such as antidepressants and tranquilizers, and NSAIDs.[3] However, some classes of drugs have notably lower ADR rates despite high rates of use. In the studies we reviewed, antihistamines and the statin drugs prescribed to lower cholesterol levels were rarely associated with serious ADRs.

Some Patients Have a Greater Risk of ADRs Than Others

Patients who are very ill, including those with several concurrent diagnoses, have a greater ADR risk than others. Not only are they more fragile but their illnesses may require several simultaneous treatments. In addition, they may be receiving more aggressive treatments that are known to entail significant risks. One study found that pediatric cancer patients undergoing chemotherapy had suffered ADRs at a rate 10 times that of other children admitted for inpatient treatment (Mitchell and others, 1988). Another study found that hospital patients in intensive care units (ICU) had 80 percent more ADRs than patients in general medical wards and that most of this difference was accounted for by the greater number of medications given the ICU patients (Bates and others, 1995a). (Controlling for the number of medications reduced the adverse event rate for ICU patients to 20 percent more than that for general medical patients.)

Some reports have found that elderly persons and women have more ADRs than younger persons and men. However, it is possible that age and gender

[3]Wolfe and others (1999) estimated 16,500 NSAID-related deaths annually among arthritis patients in the United States.

are merely related to other known risk factors instead of representing additional, independent risks of ADRs.[4] In some studies, controlling for the number of medications being taken substantially diminishes any relationship between age and ADRs (Gurwitz and Avorn, 1991). Although other studies have shown that women both use more drugs and have more ADRs than men overall, these studies did not control for illness severity and the number of different medications the patients took.

Medication Errors Are Common and Have Numerous Causes

Very few medication errors cause ADEs, either because errors are caught before the drugs are administered or because specific errors created no ill effects.[5] Nonetheless, because so many drug doses are given, an estimated quarter to half of all ADEs among hospital patients result from medication errors (Bates and others, 1995a; Classen and others, 1997).[6] For example, a 6-month hospital study found that the ADE rate was 1 for every 10,000 doses; 700,000 drug doses were given, and there were 70 injuries.[7] Although estimates of the actual effect of medication errors vary, they have led to hospital admissions, emergency department visits, and the death of hospitalized patients (Nelson and Talbert, 1996; Classen and others, 1991; Schneitman-McIntire and others, 1996).

Most medication errors in hospitals involve the prescriptions ordered by physicians and nurses' administration of drugs. Pharmacists make relatively few medication errors when they transcribe, verify, and dispense hospital prescriptions. Physicians' errors include overdosing and underdosing, prescribing drugs the patients have documented allergies to, and prescribing drugs known to interact adversely with other medications patients take. Administration errors include giving drugs other than those prescribed, giving drugs at the incorrect time, and giving patients the incorrect form of a drug, such as an injection rather than a tablet.

[4]Changes in the metabolism of drugs with age mean that dosing requirements for older persons differ from those for younger adults, complicating the determination of a proper dose. At the same time, elderly persons frequently have other concurrent illnesses and, as a result, usually take several drugs. One study of hospital admissions found that elderly patients took an average of 3.5 prescription drugs before their hospitalization (Grymonpre and others, 1988).

[5]Bates and others (1995b) found that 1 percent of medication errors lead to ADEs. If missed doses (approximately half of the errors) are excluded, then 2 percent lead to ADEs.

[6]A 1994 review by Pearson and others indicated that 30 to 80 percent of ADRs are preventable. However, the majority of the studies they cited were published before 1980, and therefore we did not include them in our review.

[7]Comments of Lucian Leape, "The Safety of Pharmaceuticals: Monitoring and Regulation," American Enterprise Institute conference, Washington, D.C., Mar. 26, 1999.

Patients' noncompliance is also a major ADE source. Outside the hospital and other health care institutions, patients are responsible for complying with their drug regimen rather than relying on health care professionals. They may underuse or overuse drugs, run out of a medication, or take medications inconsistently. Their noncompliance is an important cause of emergency department visits and hospital admissions. For example, researchers reported that 58 percent of ADEs in patients visiting one hospital's emergency department were caused by noncompliance (Dennehy and others, 1996). Another study found that 11 percent of all elderly patients admitted to a hospital were related to noncompliance (Col and others, 1990).

Sometimes, consistent patterns of medication error have resulted in the withdrawal of certain drugs from the market. Recently, for example, the manufacturer of bromfenac withdrew the drug when physicians continued to prescribe it for more than 10 days, even after FDA had warned against long-term administration. Similarly, the antihistamine terfenadine was withdrawn from the market after warnings and new labels failed to stop its use with certain other medications that could cause serious heart problems.

Some Drugs Lead to Medication Errors More Often Than Others Do

Analgesics, antibiotics, and cardiovascular and psychotropic drugs are among the classes of drugs consistently associated with medication errors. The number of errors for a drug class is a function of the error rate for the class and how often drugs in the class are used. The error rate for cardiovascular drugs is lower than that for many other drug classes; the large number of errors for this class primarily reflects the large number of patients taking these drugs. Not only are analgesics and antibiotics used frequently but their error rates are among the highest (Bates and others, 1998).

Some drugs have high medication error rates because their pharmacological properties make them difficult to use, even when administered in generally recommended doses. For instance, both the anticoagulant warfarin and the cardiac stimulant digoxin have narrow therapeutic indexes, meaning that the dosage levels for therapeutic effectiveness are close to toxic, and both require careful adjustment of dosage levels in individual patients. Known drug interactions pose additional risks, since some drugs interact in potentially dangerous ways with many other pharmaceuticals. For example, the label for warfarin

indicates clinically significant interactions with approximately a hundred other drugs.

Drugs with similar names can also lead to medication errors. Physicians may confuse names when prescribing drugs and pharmacists may do the same when dispensing them. Recently, concern has been raised about possible confusion between Celebrex, Celexa, and Cerbyx, names that look and sound alike but that represent very different drugs—a pain medication used to treat arthritis, an antidepressant, and an antiseizure drug, respectively.

Certain medications have been identified with a greater incidence of patient noncompliance, including insulin, phenytoin, and drugs in metered-dose inhalers (Dennehy and others, 1996; Prince and others, 1992).[8] Each of these medications requires careful monitoring by the patient or physician to determine when it should be given and in what dose. Consequently, the potential for noncompliance is quite high.

Little Is Known About the Incidence and Cost of ADEs

Although it is clear that a wide range of commonly used drugs cause ADEs with potentially serious consequences for patients, relatively little is known about the frequency of the ADEs. Data routinely collected on ADEs before and after drugs are marketed focus more on identifying which ADEs are associated with which drugs. Information on the overall incidence of ADEs from all drugs is limited to a few research studies that have typically examined the experience of patients in one or two specific institutions—generally hospitals or sometimes nursing homes—leaving the overall incidence of ADEs in outpatient care largely unexplored. The most broadly based information on ADE incidence comes from two studies drawing on statewide samples of hospital patients. These studies applied a particularly restrictive definition of ADE in finding a rate of 0.56 for every 100 patients admitted in Colorado and Utah and 0.72 in New York. This compares with a range of 2 to 30 ADEs per 100 admissions found in other studies with increasingly expansive definitions of ADE. Two studies of ADEs in individual nursing homes reported an incidence of 0.44 to 0.71 per patient month. Other studies have estimated the overall rate of fatalities from ADEs and the total costs of treating them, but both estimates are questionable because of gaps in the underlying data on ADE incidence rates.

[8]Phenytoin is an anticonvulsant used to control seizures in certain types of epilepsy and other conditions.

ADEs Are Often Difficult to Identify

Linking a particular symptom to a specific drug is difficult, primarily because ADEs are relatively rare for most drugs marketed in the United States and because drugs are often given to seriously ill patients whose underlying conditions manifest many symptoms. The best chance of identifying ADEs is when they show distinct effects shortly after a drug is administered.

Other ADEs can be extraordinarily difficult to detect. For example, symptoms that develop with the prolonged use of a drug require studies with long follow-up periods to determine whether ADEs have occurred. Similarly, rare adverse events require studies with very large numbers of patients to accumulate a sufficient number of problematic cases, and adverse symptoms that mimic those of a patient's underlying condition require carefully controlled clinical trials.[9]

Data on ADE Incidence Collected Routinely Before and After Drug Approval Are Not Comprehensive

Safety is a prominent concern throughout drug development, and many dangerous substances are identified and their testing is halted in the process. Nonetheless, by themselves, the results of clinical trials submitted with an application to FDA to market a drug cannot provide comprehensive information on possible adverse events (Faich, 1986). First, the number of patients typically included in preapproval clinical trials is too small to detect less frequent adverse events. According to the pharmaceutical industry, the total number of patients in such trials averages roughly 4,000 per drug. Consequently, adverse events that occur in 1 of 10,000 patients, for example, often do not appear at all in any clinical trials. In addition, the patients who are included in clinical trials are selected to obtain a clear picture of a drug's safety and efficacy and are therefore unlikely to reflect the full range of consumers who will actually use the drug. For example, participants in clinical trials usually include few elderly patients, few patients with serious illnesses other than the one the drug targets, and few patients taking many other medications. Clinical trials also usually last for a relatively short time, so that adverse events that occur with long-term treatment are not likely to be detected.

The limitations of the data on adverse events derived from clinical trials can be especially critical during a drug's initial marketing period. When a

[9]One well-known example comes from the Cardiac Arrhythmia Suppression Trial, which found that antiarrhythmia medications doubled the risk of cardiac arrest and death in heart attack survivors. This relationship was not detected in clinical practice because patients with heart disease regularly have arrhythmias and heart attacks, providing a ready alternative explanation that masked the causal role of the drugs. It has been estimated that these medications caused up to 50,000 premature deaths (see Echt and others, 1991).

drug is first available to consumers, it can be quickly prescribed to hundreds of thousands of patients who are far more heterogeneous than the patients studied in the clinical trials. Further, physicians often prescribe new drugs to patients who have not responded to older medications; thus, the initial recipients of a drug are more likely to be especially ill and unlike the patients studied in the clinical trials.

FDA's current postmarketing data collection systems for approved drugs are intended to compensate for the limitations of information from clinical trials by detecting the existence of previously unidentified ADEs. However, because FDA's Adverse Event Reporting System (AERS) relies on voluntary reports from physicians, pharmacists, patients, and others, it can uncover instances of problems but it cannot determine their incidence.[10] The same intrinsic limitation applies to the incident reporting systems that many hospitals have established to monitor adverse events, including ADEs. All such systems based on spontaneous reporting detect only a fraction of the total number of adverse events (Cullen and others, 1995). FDA's AERS includes an estimated 1 to 10 percent of adverse events (Goldman and others, 1996). In addition, the adverse events that are reported are unlikely to be representative of the much larger number of unreported events. For example, there is evidence that ADEs are reported more often to FDA if they involve a newly released drug or one sold by a company that has a relatively large postmarketing surveillance program (Baum and others, 1994). Consequently, any estimate of ADE incidence based on a spontaneous reporting system such as AERS would necessarily incorporate the biases of the data, undercounting some types of adverse events and overcounting others.

FDA, recognizing the limitations of its spontaneous reporting system, augments the data in AERS with information from other sources. If "signals" from AERS reports suggest new adverse events or an unexpectedly large number of known ADEs, FDA can gather additional information from several health maintenance organizations that have cooperative agreements with the agency to use their databases of member medical and pharmacy records to investigate issues of ADE causation and incidence. However, these databases sometimes do not have enough

[10]Health care providers and patients are not obligated to report suspected ADEs to FDA. However, they are encouraged to report events either directly to AERS or to the drug's manufacturer, and the manufacturers are required to forward all adverse event reports they receive to FDA.

patients taking a particular drug for a given medical condition to provide definitive answers to the questions that have arisen.[11]

Knowledge of Overall ADE Incidence Is Fragmentary

There is relatively little information on ADE frequency overall for all types of drugs. The data collected routinely before and after drug approval and through studies of ADEs associated with specific medications do not answer this question.[12] Appendix II describes the relatively few studies that we identified that were designed specifically to examine the overall incidence of ADEs.

One potential reason for the paucity of research in this area is the methodological challenge it presents. Determining that an adverse event occurred and that it was caused by a drug and not some other factor, such as the patient's underlying disease, is necessarily more complex when the scope of the investigation includes all possible adverse events and every drug the patient took. Researchers have to consider much more information from each patient's medical record on symptoms, diagnostic tests, and treatments.

Researchers conducting these studies have typically responded to this challenge by focusing on a narrowly defined patient population. For example, the large majority of the studies deal exclusively with patients treated in one or two specific institutions. On a practical level, this enables researchers to examine the complete medical record for hundreds of cases without having to go to multiple institutions to first obtain permission and then copy and ship the often voluminous patient records from diverse locations.

The disadvantage of focusing on institutions is that the extent to which ADEs in different treatment settings are studied is quite uneven. Researchers tend to study the type of institutions that have the most complete and detailed records, which is usually hospitals. Consequently, ADEs in other settings are examined either less often or not at all. We found

[11]Without information on the incidence of ADEs, it can be difficult for FDA to assess the level of risk a drug poses. For example, in March 1999, an FDA advisory committee considering the safety of troglitazone, a drug for type II diabetes, was unable to determine the number of patients who suffered liver failure while taking the drug. Estimates of the number of deaths and liver transplants presented by an FDA epidemiologist and the drug's manufacturer differed by tenfold.

[12]Much of the substantial literature on ADEs consists of published studies that focused on a specific drug or class of drugs. See, for example, the 239 abstracts of studies conducted by the Boston Collaborative Drug Surveillance Program listed in Jick (1992). Such studies may indicate the incidence of adverse events with a given medication or drug class, but there is no direct way to aggregate specific drugs and types of ADEs to arrive at an overall incidence rate.

only a few studies of ADEs among nursing home residents and only one small study of ADEs that occurred in the community and were treated in physicians' offices.[13] The general lack of information about the incidence of ADEs that occur and are treated outside hospitals and nursing homes means that our basing our estimates of overall ADE incidence on current knowledge necessarily limits us to institutional settings.

A related problem arises in attempting to extrapolate from the studies of overall ADE incidence in selected hospitals and nursing homes to other comparable institutions. Without evidence that the studied institutions are representative of others, it is not appropriate to project the results to patients treated in other facilities. The one or two institutions studied may differ substantially from other institutions of the same type with respect to the characteristics of the patients served or services provided, which in turn could affect the overall rate of ADEs.

ADEs Differ for Hospital Patients and Nursing Home Residents

With two exceptions, the existing studies of ADEs among hospital patients each reported data from a different individual hospital (or, in one case, two hospitals) and they frequently differed substantially in the way they defined and counted ADEs. Some studies examined how many hospital admissions stemmed from ADEs, others tracked ADEs that occurred during the course of a hospital stay, and a few did both. One study focused solely on ADRs (thereby excluding medication errors), another identified any injury caused by a drug, and several others counted any adverse experience associated with the use of a medication. Some included events that were possibly, but not definitely, caused by a drug, while others did not. All these variations help explain the range in ADE incidence reported by different studies.

The two studies with an unusually broad, statewide sample of patients but a highly restrictive definition of ADEs found rates of 0.56 and 0.72 ADEs for every 100 hospital admissions. The higher figure emerged from the Harvard Medical Practice Study (HMPS), which examined a representative sample of all nonpsychiatric patients treated in acute care hospitals in New York in 1984 (Brennan and others, 1991; Leape and others, 1991). It therefore included a proportionate mix of patients from teaching and nonteaching, urban and rural, and large and small hospitals. More recently,

[13]Klein and others (1984) was a study of 299 mostly chronically ill patients treated in outpatient clinics run by Johns Hopkins University and is therefore unlikely to reflect community-based care as a whole. There are several studies from periods before our 1980 cutoff date and from foreign countries, but this is the only one we found that examined overall ADE incidence in outpatient care that met our selection criteria—U.S. patient data from 1980 or later. However, several new studies of ADE incidence in noninstitutionalized populations are now under way.

the same methodology was applied to statewide samples of 1992 hospital discharges in Colorado and Utah (Thomas and others, forthcoming). Even though a sample of patients in one or two states is vulnerable to certain biases—such as those deriving from regional variation in clinical practice patterns—the databases for the studies that used them are far more diversified and representative than those of the other studies we examined. Moreover, the fact that the rates found in these two studies are relatively close, despite the studies' variation in time and place, suggests that regional and temporal variation in ADE incidence may not be very large. However, by counting only those ADEs that resulted in disability, prolongation of a patient's hospital stay, or death, these two studies identified just a fraction of the patients injured by drugs.[14]

Four other studies examined adverse drug events among hospital inpatients, reporting ADE incidence rates ranging from 2.0 to 30 ADEs per 100 admissions (see table II.1 in appendix II).[15] The higher rates came from the studies with more expansive definitions of ADEs. There was less variation among the studies in their reported incidence of moderate to severe ADEs, which ranged from 1.9 to 19 per 100 admissions.

Compared with hospital patients, nursing home residents are generally more frail and functionally impaired. While nursing homes are designed to provide less intensive care than hospitals, their residents still receive many medications. These factors probably increase the vulnerability of nursing home residents to ADEs. Patients also tend to stay longer in nursing homes than in hospitals, so ADE rates for nursing home residents are often reported per unit of time, such as patient months, to adjust for risk differences attributable to longer and shorter stays.

We found fewer studies of ADE incidence in nursing homes than in hospitals, and none examined more than one or two institutions.[16] As with the hospital studies, the definition of what constituted an ADE varied substantially. One study with a more narrow definition reported an incidence of 0.44 ADEs for every month that a patient spent in that institution, compared with 0.71 ADEs reported in a second study with a

[14]Bates and others (1995a), conducting a study in two Boston-area teaching hospitals, applied both the ADE definition that HMPS used and a broader ADE definition that included any injury related to a prescribed drug. The ADE incidence rate was 0.5 percent under the HMPS definition and 6.5 percent under the broader definition.

[15]It is not possible to calculate an incidence rate for studies focusing on ADE-caused admissions to a particular hospital, because there is no defined population at risk for admission to that hospital, and only that hospital, if an ADE occurs. See appendix II.

[16]A study of 18 nursing homes in eastern and central Massachusetts is under way.

much broader definition (see table II.2 in appendix II).[17] These rates are roughly comparable with the rates reported by the one study of hospital ADEs that presented ADE incidence in terms of time spent in the hospital.[18]

Estimates of Deaths Are Uncertain

Adverse drug events are sometimes so severe that patients die from them. There is little certainty about the frequency of fatal ADEs, because the data on fatalities stemming from ADEs are even more sparse than the data on overall ADE incidence. Recently, Lazarou, Pomeranz, and Corey (1998a) attempted to synthesize available data on ADR fatalities.[19] To derive their estimate of 106,000 fatal ADRs in the United States in 1994, they drew on data from 16 ADR studies published between 1964 and 1995. The studies cumulatively looked at 78 deaths, but only two of the studies had more than 10 deaths, and more than 40 percent of the deaths were reported in one 1973 study. Consequently, there were too few deaths to arrive at a stable estimate of total ADR fatalities—as even a small change in the number of deaths reported in the studies would lead to substantial changes in the number of deaths extrapolated to the national population.

In addition to the small number of deaths on which this estimate was based, there is a major question about relying on data from studies more than 20 years old. Since the 1960s and 1970s, drug therapies have shifted markedly for many conditions, with a generally more intensive use of pharmaceuticals now than in the past. Of the 16 studies that Lazarou and colleagues included in their analysis of ADE fatalities, only 4 were published after 1976. Collectively, these 4 studies accounted for a total of 5 deaths, compared with 73 in the 12 earlier studies. Thus, the projection

[17]The first study (Gerety and others, 1993) basically looked for ADRs. The second (Cooper, 1986) looked for a much larger category of drug-related problems, including any unwanted consequence of using or not using drug therapy.

[18]This study (Bates and others, 1995a) reported an overall incidence of 0.345 ADEs per patient month, ranging from 0.267 in surgical general care wards to 0.582 in medical intensive care wards. The figures were converted from events per 1,000 patient days to events per patient month.

[19]Their estimates are for fatal adverse drug reactions; they did not address fatalities caused by medication errors.

Lazarou and his colleagues made for the incidence of fatal ADEs for 1994 was actually based on the experience of patients 20 or more years earlier.[20]

Data on the Cost of Treating ADEs Are Limited

The lack of overall incidence data for ADEs in the United States impedes making a reliable estimate of the nationwide costs of adverse drug events, although several studies have reported similar costs for treating ADEs in hospitals. Researchers have followed different approaches in attempting to generate information about the direct costs of treating adverse drug events, but we found only one study that attempted to calculate indirect costs such as lost income.

Most studies of ADE costs have focused on one or two individual institutions. (See appendix III.) Three of the four studies that specifically analyzed the average excess hospital costs resulting from ADEs reported estimates ranging from $1,939 to $2,595 (Bates and others, 1997; Classen and others, 1997; Evans and others, 1994b). The outlier study reported average ADE costs of only $783 (Schneider and others, 1995). Two of these studies also extrapolated their findings on ADE incidence and costs in these particular hospitals to all hospital patients in the United States, producing estimates of $1.56 billion and $4 billion in additional hospital costs per year nationwide from ADEs (Bates and others, 1997; Classen and others, 1997). While these estimates may help indicate the general scope of ADE costs, because each is based on just one or two hospitals, their precision for estimating costs on a national level is limited.

Three other studies used expert panels to generate ADE cost estimates (Bootman, Harrison, and Cox, 1997; Johnson and others, 1995, 1997). The experts came to a collective judgment as to the likely probability of specified negative outcomes arising from drug therapy, which translated into an incidence rate for the patient population as a whole.[21] The total

[20]When Kenneth Fremont-Smith (1998) criticized Lazarou and his colleagues on this point, they responded (1998b) that they had since analyzed unpublished data from 32 additional studies of fatal ADEs in industrialized countries other than the United States. They stated that these data, when combined with the U.S. data, showed no trend in rates of fatal ADRs, either up or down over time. They also found no statistically significant difference between the U.S. and non-U.S. studies. They maintained that this demonstrated that the rate of fatal ADRs had not changed in the United States, thereby validating their original estimate. They took this approach because, in their view, the data from recent studies of fatal ADRs among U.S. hospital patients were not sufficient to derive a statistically reliable estimate of the incidence of fatal ADRs in the United States.

[21]The panel members in one of these studies were pharmacists who were selected because of their extensive clinical practice in ambulatory settings and recognition as leaders in pharmacy practice in the United States (Johnson and others, 1995). In a later study, the panel members were physicians and consultant pharmacists with practice experience in nursing facilities and geriatric care (Bootman, Harrison, and Cox, 1997).

cost of ADEs was then calculated by multiplying the estimated number of ADEs by the unit cost of treating them.[22] For one study in 1995, this process produced an estimate for the costs of drug-related morbidity and mortality in the ambulatory setting of $76.6 billion annually, primarily because of the resulting admissions to hospitals, costing $47.4 billion, and long-term-care facilities, costing $14.4 billion.[23] A later study in 1997 estimated the cost of drug-related morbidity and mortality in nursing facilities to be around $7.6 billion annually (Bootman, Harrison, and Cox, 1997). The probability statements developed by an expert panel are inherently subjective and would be likely to change if the composition of the panel changed. Since the cost estimates are based on these estimated incidence rates, the cost estimates are also open to question.

Finally, the 1999 study conducted in Colorado and Utah also collected information about the costs of adverse events, including those that were drug-related (Thomas and others, 1999). Distinguishing this study are its broad-based sample of 14,732 randomly sampled discharges from hospitals in two states and its inclusion of indirect as well as direct treatment costs for ADEs. From data extracted from the patients' medical records, physicians and malpractice claims adjusters estimated the patient's degree of disability and likely use of health care in the future. Projected inpatient and outpatient health care costs, lost wages, and lost household production were then estimated, and the total was reported as an aggregate national figure. The $5.2 billion estimate for hospital costs alone exceeded the costs reported in both of the earlier studies from individual institutions. Adding in the estimated cost of outpatient care, lost income, and lost household production brought the total of direct and indirect costs to an estimated $12.2 billion in 1996 dollars. This result is based on a much broader sample than in the earlier studies, although still limited to Colorado and Utah. In extrapolating the results to an aggregate national estimate, the authors did not attempt to adjust for the likely variation in hospital costs and personal incomes in other parts of the country.

[22]The expert panels also estimated the proportion of patients with negative outcomes who would receive various types of treatment in response, such as additional physician visits, new prescriptions, emergency department visits, nursing home admissions, and hospitalizations. The cost of each scenario was calculated as "monetary values"—obtained from published statistical series and research reports—for each type of treatment employed in that scenario, and then an aggregate cost figure was computed from the estimated total cost of each separate scenario and multiplied by its estimated probability across all patients (Johnson and others, 1995).

[23]With adjustments in the assumptions of the model, the estimates of total ADE costs ranged from $30.1 billion to $136.8 billion. (See Johnson and others, 1995.)

Measures Intended to Reduce the Number and Severity of Adverse Drug Events

Increased understanding of what makes ADEs likely has led researchers and patient safety advocates to develop a variety of measures intended to decrease their number and severity. The approaches they have suggested to reduce ADRs include improving communication between patients and physicians about the risks and benefits of medications, as well as expanding and accelerating research on the safety of marketed drugs to reduce the time it takes to detect previously unknown ADRs and determine the risk factors that identify the patients who are most likely to experience them. Measures designed to reduce the number of medication errors include developing computerized prescribing and dispensing systems to detect errors, avoiding confusing names and packaging, increasing the role of pharmacists as advisers to physicians in prescribing drugs and in monitoring drug therapy, and improving physicians' pharmaceutical education.

Drug Development and Better Information to Reduce ADRs

Some have suggested that the process of drug research and development could help reduce ADRs as pharmaceutical companies respond to market incentives by developing new medications with fewer risks than the ones they replace. For example, a new generation of NSAIDs called cox-2 inhibitors has recently reached the market; these drugs were designed specifically to lower the risk of gastrointestinal injury compared with traditional anti-inflammatory drugs such as aspirin or ibuprofen. Similarly, while the first in a new class of diabetes drugs, troglitazone, approved for marketing in 1997, has been associated with rare cases of deadly liver failure, FDA has since approved other drugs with similar clinical benefits but less liver toxicity (although they may have other serious side effects).

Others have suggested that physician's education—and communication between physicians and patients—about the benefits and risks of particular drugs be improved in order to promote informed decisionmaking about pharmaceuticals and thereby help reduce the incidence of ADRs. Given the large number of drugs on the market and the voluminous information about each one, some observers have suggested that computerized systems could be designed to help remind physicians when they submit prescriptions about important therapeutic considerations, including comparative benefits, risks, and contraindications for several similar drugs.

Expanded surveillance programs to gather information about marketed drugs might also help prevent ADRs by more quickly accumulating information about them for particular drugs. For example, FDA has

proposed for discussion several methods of rapidly gathering information during the crucial period following a drug's approval for marketing. These ideas include establishing a network of health care facilities to serve as "sentinel sites" for closely monitoring the experiences of the first patients to take a new drug and slowing down the introduction of new drugs until sufficient information has been collected about their risks once they are on the market.[24] Quantified risk data about new drugs could assist physicians and patients to make more informed treatment choices.

Data collection efforts that document patient risk factors for adverse events have the effect of moving some ADRs into the category of preventable medication errors. For example, reports of cardiovascular complications from using sildenafil surfaced after its approval in 1998, ultimately causing a change in the product's label to warn physicians about its dangers for patients with certain preexisting conditions. Patients with these conditions who took sildenafil and suffered an adverse cardiovascular event when the drug was first marketed might have been then classified as suffering an ADR but today would probably be considered victims of medication error.

Measures to Reduce Medication Errors

Numerous measures to reduce medication errors have been taken, and experts have proposed others for drug manufacturers and health care providers—many aiming to make errors more difficult across a range of specific circumstances. For instance, computer systems can screen prescriptions to detect errors in dosage levels or known allergies. Some proposed measures, such as eliminating look-alike packaging, would make it physically harder to dispense or administer the wrong drug. Table 1, which is meant to be illustrative rather than comprehensive or evaluative, describes a number of general approaches.

[24]The benefits of slowing down the marketing of new drugs must be weighed against the health costs of potentially restricting patients' access to them.

Table 1: Current and Proposed Approaches to Reduce Medication Errors

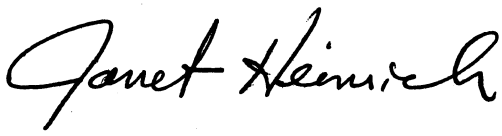
Approach	Intended benefit
Dispensing change	
Physicians' direct computer entry of prescriptions	Physicians' entering prescriptions on a computer rather than writing them reduces transcription errors and indicates potentially problematic prescriptions. For instance, it can indicate an improper dose that is being prescribed or a drug that might interact with another medication the patient is taking.
Unit dosing	Dispensing drugs from the pharmacy in single-unit or unit-dose packages (for instance, blister packs) makes them ready to administer.
Automated hospital dispensing systems	Such systems notify nurses when a drug is to be administered and allow access only to it. The systems also record what has been given and when as well as reducing delays in giving patients their medications and decreasing other administration errors.
Bar coding hospital medications	Machine-readable labels can facilitate matching patients with their prescribed medications and documenting drug dispensing and administration.
Focus on high-alert drugs	Specific systems and educational initiatives minimize errors with the drugs that have the greatest potential to cause serious harm when used incorrectly, such as insulin, opiates and narcotics, potassium chloride concentrate, and intravenous anticoagulants.
Packaging and physical change	
Differentiated drug names	Giving drugs whose names sound alike (for example, Celebrex, Celexa, and Cerbyx) different names could reduce the likelihood of their being confused.
Differentiated packaging	Packaging different drugs differently would make them easily distinguished.
Standardized packaging	Uniform labels with standards for print size and color would help practitioners and patients know where to look for particular information.
One name and one look for each drug	Drugs would be less easily confused if each one had only one name, not a generic and a brand name, and two or more manufacturers who made the same drug gave the pills the same design, packaging, and labeling.
Change in sensitivity to ADEs	
Physicians' education	Educating physicians about pharmaceuticals more, both during and after medical school, would improve their prescribing practices.
Greater pharmacist involvement	Including pharmacists in hospital rounds helps physicians make prescribing decisions, and increasing the role of community pharmacists in monitoring drug therapies improves patients' compliance.
Timely communication	Timely feed back on ongoing ADEs could help physicians in hospitals prevent the progression of ADEs to more severe forms.
Computerized ADE monitoring	Computer programs designed to screen for potential ADEs, using data from electronic inpatient or outpatient medical records, such as orders for known antidotes or specific laboratory test abnormalities, cut their number and frequency.
Culture change	
Encouraged reporting	Changing an institution's culture so that errors are seen as an indication of where systemic improvements are needed rather than simply assigning blame to individuals would make it more likely that mistakes would be reported.

Agency Comments

We provided a draft of this report to the Commissioner of FDA and five outside experts, including physicians, pharmacists, and epidemiologists who are actively involved in analyzing ADEs. FDA responded that the report accurately describes the current status of adverse event reporting. The agency also provided technical comments that we incorporated as appropriate. The outside experts generally found that our characterization of currently available information on ADEs is accurate and thorough. However, several of them expressed concern that our critical assessment of existing studies might create the misperception that there is little evidence that ADEs pose a substantial health risk to patients. We revised sections of the report and its title to make clear that while the magnitude of the health risk is uncertain its existence is not. Other comments from the experts led us to make additional corrections and clarifications to the text.

As we arranged with your office, unless you publicly announce the contents of this report earlier, we plan no further distribution of it until 30 days after its issue date. We will then send copies to the Secretary of the Department of Health and Human Services, the Commissioner of FDA, and others who are interested. We will also make copies of the report available to others on request.

If you or your staff have any questions, please contact me at (202) 512-7114. Robert M. Copeland, Martin T. Gahart, Michele Orza, Eric A. Peterson, and Helene F. Toiv were the major contributors to this report.



Janet Heinrich
Associate Director, Health Financing
and Public Health Issues

List of Requesters

The Honorable James M. Jeffords
Chairman
The Honorable Edward M. Kennedy
Ranking Minority Member
Committee on Health, Education, Labor, and Pensions
United States Senate

The Honorable Bill Frist
Chairman
Subcommittee on Public Health
Committee on Health, Education, Labor, and Pensions
United States Senate

The Honorable Richard J. Durbin
The Honorable Jack Reed
United States Senate

The Honorable Thomas J. Bliley, Jr.
Chairman
The Honorable John D. Dingell
Ranking Minority Member
Committee on Commerce
House of Representatives

The Honorable Henry A. Waxman
Ranking Minority Member
Committee on Government Reform
House of Representatives

Contents

Abbreviations

ADE	Adverse drug event
ADR	Adverse drug reaction
AERS	Adverse Event Reporting System
FDA	Food and Drug Administration
HMPS	Harvard Medical Practice Study
ICU	Intensive care unit
NSAID	Nonsteroidal anti-inflammatory drug
WHO	World Health Organization

Objectives, Scope, and Methodology

The objectives of this report were to (1) describe the different types and causes of adverse drug events (ADE), (2) examine the evidence on the overall incidence and cost of ADEs in the United States, and (3) describe measures that have been proposed to reduce the number and severity of ADEs.

This study concerns only prescription medicines. We did not examine vaccines or other biologics, medical devices, procedures, or nonprescription or illicit drugs. The study encompasses both adverse events that result from the intrinsic pharmacological characteristics of drugs and those that stem from mistakes that physicians, nurses, pharmacists, other health professionals, and patients make in using pharmaceuticals. We focused on obtaining information about the use of prescription drugs in the United States since 1980 across the full range of treatment settings, including hospitals, long-term care institutions, and outpatient facilities. We chose 1980 as the cutoff because many drugs in use now were not available before then and, for many major clinical conditions, the main classes of drugs relied on now did not exist before 1980. The results obtained in studies conducted before 1980 may have little applicability for current clinical practice. In describing proposed measures to reduce ADEs, we did not attempt to evaluate their potential effectiveness.

To identify published studies that were relevant to our study questions, we pursued three primary strategies. First, we searched computerized bibliographic databases, including Medline and Embase, for citations related to ADEs or reactions and medication error. Second, we consulted with academic researchers specializing in this area and obtained their recommendations for useful studies (see appendix IV for a list of the outside experts we consulted). Third, we examined the footnotes of the studies thus identified for leads to additional relevant studies. We then selected studies for more intensive analysis. They consist of the studies that presented primary data on the incidence of and factors related to ADEs in the United States after 1980.

We used a standardized data abstraction form to collect categories of information: how ADE (or some other corresponding term) was defined in the study, the types and severity of events observed; the relative frequency of events for different classes of drugs; the demographic and clinical characteristics of the patients experiencing the ADEs; the characteristics of the overall study population, including the number of subjects and institutions (for example, hospitals or nursing homes); how the subjects

and institutions were selected; data sources; completeness of the data; and the procedures used to attribute an adverse event to a drug and to identify medication errors. We selected these data elements to address two questions. First, what did the study have to say about the frequency and characteristics of ADEs? Second, what limitations applied to that information in terms of the population groups and institution types to which its results applied, as well as any uncertainties about the results that could derive from the way the study was conducted? Having made these assessments, we drew on the most appropriate studies to address each of our three objectives.

We obtained additional data for this study in meetings and interviews with Food and Drug Administration (FDA) officials and academic, industry-based, and other experts in the field. We initiated this process with a public forum on postmarketing surveillance, which we organized in conjunction with the Drug Information Association's Conference on Adverse Event Reporting in Washington, D.C., on February 24, 1999. Invited participants included ADE experts with a range of institutional affiliations (see appendix IV). The conference and interviews provided us with background information on the drug approval and postmarketing surveillance processes, information on proposals to reduce the incidence of and research on ADEs that had not yet been published, and clarification on several methodological issues.

Estimating the Overall Incidence of Adverse Drug Events

This appendix examines the strengths and limitations of available data on the overall incidence of ADEs. It explains why much of the information currently collected on ADEs does not pertain to the question of overall incidence. It describes the few research studies that have addressed ADE incidence in various treatment settings: hospitals, nursing homes, and emergency departments. The characteristics of these studies, in particular their nearly universal focus on one or two individual institutions, determine the limitations of current knowledge on the overall frequency of ADEs.

The Few Studies That Estimate ADE Incidence Measure It in Specific Settings

Most of the studies on ADEs assess the risks associated with individual drugs or classes of drugs—they do not estimate overall incidence. In particular, a large number of studies have involved checking whether specific events such as liver failure or allergic reactions that appeared in case reports about a drug are in fact linked to the use of that drug among larger numbers of patients. Much of the work sponsored by pharmaceutical companies and FDA falls into this category.

Other studies that have examined ADEs more broadly have used data that are not appropriate for incidence calculations. For example, some researchers have examined ADEs by using data from the incident reporting systems that virtually all hospitals maintain. These systems compile reports of adverse events submitted by hospital staff members, including those involved in drug therapy. The key limitation of all such spontaneous reporting systems with regard to estimating ADE incidence is that the cases that any one person chooses to report probably differ substantially from the much larger number of unreported events.

This leaves a relative handful of studies that attempted to collect primary data on the full range of ADEs experienced by a defined patient population. Their small number reflects the complexity of the task. It can often be difficult to distinguish adverse events caused by a drug from those caused by the medical conditions that the drugs are intended to treat. To do this requires either a careful review of the medical record for each case included in the study or, preferably, a means of monitoring a patient's care as it is provided in order to identify and verify ADEs when they occur. As a practical matter, it is most feasible to do this in specific institutional settings. Therefore, the studies that have produced data on the incidence of ADEs are restricted by having focused on a particular treatment setting—for example, hospitals and nursing homes—and in most cases to one or two specific providers.

Studies of Hospitals Vary Substantially

The six studies we found that systematically collected primary data on ADEs occurring during a hospital stay vary substantially along multiple dimensions.[25] (See table II.1.) First, they define ADEs very differently. The Harvard Medical Practice Study (Brennan and others, 1991) and its replication in Colorado and Utah (Thomas and others, forthcoming) counted only quite severe adverse events, whereas several others had no severity threshold. The Brennan and Thomas studies and, to a lesser extent, Classen (Classen and others, 1991) included some cases in which an ADE was present on admission rather than just cases that developed during the hospital stay under study. Classen used the World Health Organization (WHO) definition of an adverse drug reaction (ADR), which excludes adverse effects produced by doses outside the normal therapeutic range.[26] The other studies focused on events caused by drug therapy, whatever the dosage.

[25]These studies attempted, within their given institutional focus, to capture the experience of a broad range of patients in terms of demographics and clinical conditions. Numerous other studies focus exclusively on various patient subgroups—such as children, the elderly, patients with psychiatric conditions, and patients receiving specific drugs or experiencing specific types of ADEs—that we judged to be less useful for assessing the overall incidence of ADEs.

[26]WHO defines ADR as the noxious and unintended effects of a drug that occur at doses used in humans for prophylaxis, diagnosis, or therapy. This definition excludes some medication errors (such as accidental overdoses) but includes others (such as prescribing the wrong drug).

Table II.1: Six Studies of Hospital Inpatient ADEs

ADE definition	ADE type	ADEs per 100 admissions	Study size	Site studied
Thomas and others, forthcoming				
Injury caused by medical management resulting in prolonged hospitalization or disability at discharge[a]	Inpatient and admission	0.56	14,700	All wards except psychiatric in a stratified sample of acute care hospitals in Colorado and Utah
Brennan and others, 1991				
Unintended injury caused by medical management resulting in measurable disability or prolonged hospitalization[a]	Inpatient and admission	0.72	31,429	All wards except psychiatric in a representative sample of New York State acute care hospitals
Classen and others, 1991				
Any noxious, unintended, and undesired effect of a drug that occurs at doses used in humans for prophylaxis, diagnosis, or therapy	Inpatient[b]	1.99 (1.91 moderate or severe)	36,653	All wards in one acute care referral center and teaching hospital in Utah
Bates and others, 1995a				
An injury resulting from administering a drug	Inpatient	6.5 (2.8 serious, life-threatening, or fatal)	4,031	Medical, surgical, and intensive care units (ICU) in two tertiary care hospitals in the Boston area
Steel and others, 1981				
Any illness resulting from a diagnostic procedure or from any form of therapy[a]	Inpatient	25.5 (4.91 life-threatening or fatal)	815	Medical, medical ICU, and coronary care unit at one university teaching hospital in Boston
Bowman and others, 1994				
Any adverse experience associated with the use of a drug, including experiences rated “possible” on the Naranjo scale	Inpatient	29.7 (18.7 moderate or severe)	1,024	Internal medicine and ICU at one county general hospital in Indiana

[a]We extracted from this definition the injuries that drugs caused.

[b]Seven percent of reported ADEs were present at admission.

The studies also differed in their approach and intensity of data collection. The Brennan and Thomas studies were strictly retrospective reviews of medical records. The four other studies in table II.1 all collected data prospectively (while patients were undergoing treatment), although Classen first screened cases by applying computer algorithms to patients’ records in order to identify the cases most likely to experience an ADE.

Prospective data collection meant that information from a medical record could be supplemented with interviews with the staff who cared for a particular patient.

Differences in the studies' definitions affected the ADE rates they found. The two studies with the apparently least restrictive definitions, Steel and Bowman, reported the highest rates. Similarly, the differences in the studies narrow substantially when the rates from the Brennan and Thomas studies are compared with those for the more severe cases in the other studies.

In contrast, there is no apparent relationship between type of hospital (university or teaching versus community) and rates of observed ADEs. The three studies of individual university hospitals varied from one another by a wide margin. Meanwhile, the single available study of a community hospital (Bowman) had the highest reported rate, while the Brennan and Thomas studies, which combined both teaching and nonteaching hospitals (but did not break them out separately for ADEs), had the lowest rates. These variations may largely reflect differences on other dimensions (for example, the definition of ADE) as well as potentially large variations across individual institutions. Whether teaching or community hospitals are likely to have higher ADE rates remains an open question.

Studies of Nursing Homes Suggest That ADEs Are Common Among Residents

Nursing home residents, like hospital patients, are typically sick or frail and receive many medications, circumstances that would tend to increase their vulnerability to ADEs. Indeed, the three small-scale studies we identified that sought to measure the incidence of ADEs in nursing homes were all quite consistent in finding a high prevalence of ADEs. (See table II.2.)

Table II.2: Three Studies of ADEs in Long-Term-Care Facilities

ADE definition	ADEs per patient-month	Study size	Site studied
Gerety and others, 1993			
Known reaction to drug, appropriate temporal sequence, no alternative explanation (Naranjo algorithm)	0.44 (115 per 100 admissions)	175	One university-affiliated Department of Veterans' Affairs nursing home
Cooper, 1996			
Any noxious and unintended effect of a drug that occurs at doses used in humans for prophylaxis, diagnosis, or therapy judged at least "probable" on the Naranjo scale	134 per 100 admissions[a]	332	Two rural nursing homes
Cooper, 1986			
Drug-related problem, any unwanted consequence from using or not using drug therapy	0.71 (1,200 per 100 admissions)	102	One long-term-care facility attached to a small community hospital

[a]ADEs not reported per month.

As in the studies of inpatient ADEs, the definition of ADE varied widely. It could include not only the kinds of events considered to be an ADE—for example, Cooper (1986) counted an inability to pay for prescribed medications—but also the degree of certainty required that a drug had caused the event in question. The two other studies, with narrower definitions, reported markedly lower rates, but even they found that a majority of nursing home residents experienced ADEs.[27]

The Data on Emergency Department Visits and Hospital Admissions Are Insufficient for Estimating Overall ADE Frequency

Unlike ADE rates for inpatient and long-term care, which apply to events in the specific institutions where the data are collected, ADE rates reported for emergency department visits and hospital admissions relate to care that previous health care providers have already given to patients. The rates reported for inpatient ADEs have quite a different meaning from those presented in either studies of emergency department visits or hospital admissions. The former report on the probability that an individual patient will experience an ADE, while the latter focus on the proportion of emergency department and hospital patient volume brought about by ADEs. Studies of emergency department visits and hospital admissions differ primarily in level of severity. The first examine ADEs serious enough to

[27]The substantial variation in both the ADE rates reported and the definitions employed, combined with the small number of institutions and patients studied, leaves considerable uncertainty about the specific rate of ADEs among nursing home residents. A more precise estimate would require one or more larger-scale studies that assessed the frequency of ADEs across multiple facilities. One such assessment is under way in 18 nursing homes in central and eastern Massachusetts.

motivate an emergency department visit, while the second are about patients whose ADEs required inpatient care.

To use data from studies of emergency department visits and hospital admissions to estimate an overall rate of ADEs for a given population, two requirements must be satisfied. First, the data must be from all the hospitals serving the targeted population or at least from a representative sample. Second, additional data have to be collected on ADEs that took place during a hospital episode and were treated in the hospital where they occurred. Patients transferred to another hospital to treat an ADE would normally appear in the admissions data for the receiving hospital, but those treated for ADEs in the hospital where they occurred would not be associated with any admission.[28]

Each study that we found on emergency department visits and hospital admissions for ADEs was limited to a single institution. (See tables II.3 and II.4.) The rates these studies reported, therefore, depend on the particular mix of patients each hospital attracted relative to the alternative providers available in its geographic area. Without information about ADE admissions to other hospitals in these areas, there is no way of knowing how similar the rates the studies reported are to those prevailing among other providers.

[28]The results of the Harvard Medical Practice Study suggest that a large proportion of serious ADEs occur and are treated during the same hospitalization. Although separate figures for drug-related adverse events were not reported, for adverse events overall, 49 percent were in this category. Most of the remaining adverse events would appear as hospital admissions, including 31 percent that occurred during a previous hospitalization and 15 percent that occurred in an outpatient setting (Brennan and others, 1991, p. 373).

Table II.3: Four Studies of Emergency Department Visits for ADEs

ADE definition	ADEs per 100 visits	Study size	Site studied
Schneitman-McIntire and others, 1996			
•Unfavorable effect of drug use plus poor compliance, inappropriate self-medication, inappropriate prescribing, and drug interactions	1.73	62,216	The emergency department of a health maintenance organization medical center in Walnut Creek, Calif.
•ADR: undesired adverse effects + allergy + drug interactions	1.23		
•Hospital admission for ADE	0.244		
Prince and others, 1992			
•Drug-related illness	2.88	10,184	One tertiary care hospital in Pittsburgh, Penna.
•ADR: undesirable event reasonably and temporally associated with the use of a drug at normal doses + drug interactions	0.815		
•Hospital admission for drug-related illness	0.697		
Dennehy and others, 1996			
•Drug-related illness	3.97	1,260	One university teaching hospital in San Francisco, Calif.
•ADR: noxious and unintended effect or the result of drug therapy	1.27		
•Hospital admission for drug-related illness	0.635		
Smith and others. 1997			
•Drug-related problem	4.24	5,757	One university teaching hospital in Lexington, Ky.
•ADR: any undesirable or unexpected drug-related event + drug interactions	0.469		
•Hospital admission for drug-related problem	0.625		

Table II.4: Four Studies of Hospital Admissions for ADEs

ADE definition	ADE rate among hospital admissions	Study size	Site studied
Lakshmanan and others, 1986			
Admission for adverse reactions to medical therapy, surgery, or diagnostic procedures[a]	4.2%	834	Medical, ICU, and oncology wards at one public teaching hospital in Cleveland, Ohio
Nelson and Talbert, 1996			
Known reaction to drug; appropriate temporal sequence; no alternative explanation (Naranjo and Hallas algorithms)	5.3	452	Medical, cardiac, and ICU wards at one university-affiliated county hospital in Bexar County, Tex.
Bigby and others, 1987			
Hospital admission from emergency department with ADE, ADE not defined	6.9	686	One teaching hospital in Cambridge, Mass.
Colt and Shapiro, 1989			
Undesired or unintended response to medication at appropriate dosage for prophylaxis, diagnosis, or therapy	9.4	244	Medical ward at one community teaching hospital in Pittsburgh, Penna.

[a]We extracted from this definition the injuries that drugs caused.

Whatever the differences in patient populations examined in these studies, they reported relatively consistent ADE rates. This may stem in part from the fairly uniform definition of ADE they applied. For emergency department visits, the studies stated that around 2 to 4 percent involved a rather broad category of drug-related illness or problems, while approximately 1 percent related to ADRs more narrowly defined. The range in studies of hospital admissions is somewhat wider and higher—roughly 4 to 9 percent. The fairly diverse hospitals, both geographically (California, Pennsylvania, and Texas) and in institutional affiliation (public, private community, university, and health maintenance organization), yielded relatively consistent results.

Nevertheless, none of these studies provides information as complete on the full range of ADEs as do the Brennan and Thomas studies. They alone both build on a sample representative of a broad-based population (if still short of nationwide) and have a data collection approach that encompasses ADEs wherever they occur—during a hospital stay or before admission, either in another hospital or in an outpatient setting. The only ADEs missed in the Brennan and Thomas studies are those that were not treated in a hospital. They would also be missed in all the other studies,

except by studies of patients with ADEs who made emergency department visits.

Sixteen Studies Estimating ADE Costs in the United States

Study	Site	Eligible patients	Method	Cost estimate
Bates and others, 1997	Brigham and Women's Hospital and Massachusetts General Hospital, Boston, Mass.	All 4,108 patients admitted to a stratified random sample of medical and surgical units and intensive care and nonintensive care units; excluded obstetric units	Compare comparable patients with ADEs to those without	An increased hospital cost of $2,595 per ADE and $4685 per preventable ADE; $5.6 million per year in additional costs with $2.8 million attributable to preventable ADEs
Bootman, Harrison, and Cox, 1997	Nursing facilities (no specific sites studied)	No patients studied	Expert panel estimated ADE rates and treatments needed	$7.6 billion in costs to third-party payer from drug-related morbidity and mortality in nursing homes
Classen and others, 1997	LDS Hospital, Salt Lake City, Utah	All 91,574 hospital admissions	Compare comparable patients with ADEs to those without	Hospital cost of $2,013 per ADE; 4-year cost of $4,482,951 (excludes liability costs and the cost of injury to patients)
Col and others, 1990	Unspecified community teaching hospital	315 consecutively admitted elderly patients	Assess ADRs in patients who experienced them; no comparison group	Hospital cost of $2,147 per patient admitted with ADE related to noncompliance (total cost of $77,289 for 3 months); cost of $4,237 per patient admitted with ADR (total cost of $224,542 for 3 months)
Cooper, 1987	Unspecified nursing home	All residents; sample of 6 cases of ADEs to generate cost estimate	Assess ADRs in patients who experienced them; no comparison group	$3,749 per episode that resulted in hospitalization; up to $340,942 in costs could have been avoided over a 2-year period.
Cullen and others, 1997	Brigham and Women's Hospital and Massachusetts General Hospital, Boston, Mass.	All 4,031 patients admitted to sample of intensive care and general care units	Comparisons between patients who had first ADE in the ICU and the remaining ICU patients and between medical and surgical patients with an ADE	Costs after ADE of $9,192 per ADE in surgical general care unit, $17,437 in medical general care unit, $17,577 in medical intensive care unit, and $20,959 in surgical intensive care unit; total cost $1,366,840 over 6 months
Dennehy and others, 1996	University of California, San Francisco	1,260 emergency department patients (68 percent of all emergency department patients)	Assess ADEs in patients who experienced them; no comparison group	Hospital costs of $283 for patients with ADE who were not hospitalized, $2,815 for those who were; $308 for patients with preventable ADEs not hospitalized, $2,752 for those who were; total annual cost $602,597, with $391,342 coming from avoidable ADEs
Evans and others, 1993	LDS Hospital, Salt Lake City, Utah	All hospitalized patients	Compare patients with ADEs to those without	Average cost of hospitalization for patients with ADEs from allergic or idiosyncratic reactions was $30,617, from known toxicities $23,256; average cost for patients without ADEs was $6,320

(continued)

Study	Site	Eligible patients	Method	Cost estimate
Evans and others, 1994b	LDS Hospital, Salt Lake City, Utah	All 60,836 hospitalized patients	Compare comparable patients with ADEs to those without	$1,939 higher cost for patients with an ADE than for those without; total annual cost of $1,103,291
Johnson and others, 1995	Unspecified ambulatory settings	No patients studied	Expert panel estimated ADE rates and treatments needed	$76.6 billion in annual costs to third-party payers associated with management of drug-related mortality and morbidity
Johnson and others, 1997	Unspecified ambulatory settings	No patients studied	Expert panel estimated ADE rates and treatments needed	$45.6 billion savings for third-party payers if pharmaceutical care was instituted nationwide, a 59.6 percent reduction from $76.6 billion
Prince and others, 1992	Mercy Hospital, Pittsburgh, Penna.	All 10,184 emergency room visits	Assess ADEs in patients who experienced them; no comparison group	Average hospital charge per admission for a patient with an ADE was $8,888; total annual cost of $631,048
Schneider and others, 1995	Ohio State University Medical Center, Columbus, Ohio	109 patient charts reviewed; selection criteria not stated	Assess ADEs in patients who experienced them; no comparison group	Average institutional cost of $783 per ADE; total annual cost of $1,497,148
Stoukides, D'Agostino, and Kaufman, 1993	Roger Williams Medical Center, Brown University, Providence, R.I.	All 13,703 emergency room visits	Assess ADEs in patients who experienced them; no comparison group	Average cost of $333.81 per emergency department visit; total cost of $39,389.58 for 6 months
Sullivan, Kreling, and Hazlet, 1990	Unspecified hospitals (based on other studies)	2,942 hospital admissions from seven studies reviewed	Metaanalysis	$8.5 billion spent on hospitalizations in 1986 because of noncompliance
Thomas and others, 1999	28 hospitals in Colorado and Utah	14,732 randomly selected hospital discharges	Physicians and malpractice claims adjusters estimated the extent of disability and future health care use from data from medical records of patients with ADEs	$5.2 billion hospital costs to treat ADEs nationwide; $12.2 billion, including outpatient care, lost wages, and lost household production

Experts We Consulted

David Bates, M.D., Chief, Division of General Medicine, Brigham & Women's Hospital, Boston, Mass.[29]

J. Lyle Bootman, Ph.D., Executive Director, Center for Health Outcomes and PharmacoEconomic Research, College of Pharmacy, University of Arizona, Tucson, Ariz.

Michael R. Cohen, M.S., President, Institute for Safe Medication Practices, Huntingdon Valley, Penna.

Nancy A. Dreyer, Ph.D., Chief Executive Officer, Epidemiology Resources Inc., Newton Lower Falls, Mass.

David I. Goldsmith, M.D., Senior Medical Director, Safety Surveillance, Sanofi Pharmaceuticals, New York, N.Y.[29]

Hershel Jick, M.D., Director, Boston Collaborative Drug Surveillance Program, Lexington, Mass.

Judith K. Jones, M.D., Ph.D., President and Chief Executive Officer, The Degge Group, Arlington, Va.[29]

Lucian Leape, Ph.D., Professor, Harvard School of Public Health, Boston, Mass.

Murray M. Lumpkin, M.D., Deputy Center Director, Center for Drug Evaluation and Research, U.S. Food and Drug Administration, Rockville, Md.[29]

Henri R. Manasse, Jr., Ph.D., Sc.D., Executive Vice President and Chief Executive Officer, American Society of Health-System Pharmacists, Bethesda, Md.[29]

Thomas J. Moore, Fellow, Center for Health Policy Research, School of Public Health and Health Services, George Washington University, Washington, D.C.[29]

Robert C. Nelson, Ph.D., RCN Associates, Annapolis, Md., and Chair, Committee on Quality Data for Risk Assessment of Drugs, International Society for Pharmacoepidemiology, Washington, D.C.[29]

[29]Invited participant at the joint General Accounting Office and Drug Information Association session, "Postmarketing Surveillance: Considerations for Policymakers," conference on Adverse Event Reporting: From Theory to Practice, Washington, D.C., Feb. 24, 1999.

Richard Platt, M.D., Director of Research, Harvard Pilgrim Healthcare, Boston, Mass.

Larry D. Sasich, Pharm.D., M.P.H., Research Analyst, Public Citizen's Health Research Group, Washington, D.C.[30]

Judith M. Sills, Pharm.D., Senior Director, U.S. Regulatory Affairs and Global Product Safety, Warner-Lambert Consumer Healthcare, Morris Plains, N.J.[30]

Bert Spilker, M.D., Ph.D., Senior Vice President for Scientific and Regulatory Affairs, Pharmaceutical Research and Manufacturers of America, Washington, D.C.[30]

Brian Strom, M.D., M.P.H., Director, Center for Clinical Epidemiology and Biostatistics, University of Pennsylvania, Philadelphia, Penna.[30]

Eleanor M. Vogt, R.Ph., Ph.D., Senior Fellow, National Patient Safety Foundation, American Medical Association, Washington, D.C.[30]

Ray Woosley, M.D., Ph.D., Chairman, Department of Pharmacology, Georgetown University Medical Center, Washington, D.C.[30]

[30]Invited participant at the joint General Accounting Office and Drug Information Association session, "Postmarketing Surveillance: Considerations for Policymakers," conference on Adverse Event Reporting: From Theory to Practice, Washington, D.C., Feb. 24, 1999.

Bibliography

Allan, E.L., and others. "Dispensing Errors and Counseling in Community Practice." American Pharmacy, Vol. NS35 (1995), pp. 25-33.

Barker, K.N., and others. "Consultation Evaluation of a Hospital Medication System: Analysis of the Existing System." American Journal of Hospital Pharmacy, Vol. 41 (1984), pp. 2009-16.

Bates, D.W., and others. "Incidence and Preventability of Adverse Drug Events in Hospitalized Adults." Journal of General Internal Medicine, Vol. 8 (1993), pp. 289-94.

Bates, D.W., and others. "Incidence of Adverse Drug Events and Potential Adverse Drug Events: Implications for Prevention." Journal of the American Medical Association, Vol. 274, No. 1 (1995a), pp. 29-34.

Bates, D.W., and others. "Relationship Between Medication Errors and Adverse Drug Events." Journal of General Internal Medicine, Vol. 10 (1995b), pp. 199-205.

Bates, D.W., and others. "The Costs of Adverse Drug Events in Hospitalized Patients." Journal of the American Medical Association, Vol. 277, No. 4 (1997), pp. 307-11.

Bates, D.W., and others. "Effect of Computerized Physician Order Entry and a Team Intervention on Prevention of Serious Medication Errors." Journal of the American Medical Association, Vol. 280, No. 15 (1998), pp. 1311-16.

Baum, C., and others. "The Spontaneous Reporting System in the United States." In B.L. Strom, ed. Pharmacoepidemiology, 2nd ed. New York: John Wiley and Sons, 1994.

Beers, M.H., M. Storrie, and G. Lee. "Potential Adverse Drug Interactions in the Emergency Room: An Issue in the Quality of Care." Annals of Internal Medicine, Vol. 112 (1990), pp. 61-64.

Beers, M.H., and others. "Inappropriate Medication Prescribing in Skilled-Nursing Facilities." Annals of Internal Medicine, Vol. 117 (1992), pp. 684-89.

Bero, L.A., H.L. Lipton, and J.A. Bird. "Characterization of Geriatric Drug-Related Hospital Readmissions." Medical Care, Vol. 29, No. 10 (Oct. 1991), pp. 989-1003.

Bigby, J., and others. "Assessing the Preventability of Emergency Hospital Admissions: A Method for Evaluating the Quality of Medical Care in a Primary Care Facility." The American Journal of Medicine, Vol. 83 (1987), pp. 1031-36.

Bootman, J.L., D.L. Harrison, and E. Cox. "The Health Care Cost of Drug-Related Morbidity and Mortality in Nursing Facilities." Archives of Internal Medicine, Vol. 157 (1997), pp. 2089-96.

Bowman, L., and others. "Incidence of Adverse Drug Reactions in Adult Medical Inpatients." Canadian Journal of Hospital Pharmacy, Vol. 47 (1994), pp. 209-16.

Brennan, T.A., and others. "Incidence of Adverse Events and Negligence in Hospitalized Patients: Results of the Harvard Medical Practice Study I." New England Journal of Medicine, Vol. 324, No. 6 (1991), pp. 370-76.

Classen, D.C., and others. "Computerized Surveillance of Adverse Drug Events in Hospital Patients." Journal of the American Medical Association, Vol. 266 (1991), pp. 2847-51.

Classen, D.C., and others. "Adverse Drug Events in Hospitalized Patients: Excess Length of Stay, Extra Costs, and Attributable Mortality." Journal of the American Medical Association, Vol. 277, No. 4 (1997), pp. 301-06.

Col, N., and others. "The Role of Medication Noncompliance and Adverse Drug Reactions in Hospitalizations of the Elderly." Archives of Internal Medicine, Vol. 150 (1990), pp. 841-45.

Colt, H.G., and A.P. Shapiro. "Drug-Induced Illness as a Cause for Admission to a Community Hospital." Journal of the American Geriatrics Society, Vol. 37 (1989), pp. 323-26.

Cooper, J.W. "Drug-Related Problems in a Geriatric Long Term Care Facility." Journal of Geriatric Drug Therapy, Vol. 1 (1986), pp. 47-68.

Cooper, J.W. "Adverse Drug Reactions and Interactions in a Nursing Home." Nursing Homes and Senior Citizen Care," Vol. 36 (1987), pp. 7-11.

Cooper, J.W. "Probable Adverse Drug Reactions in a Rural Geriatric Nursing Home Population: A Four-Year Study." Journal of the American Geriatrics Society, Vol. 44 (1996), pp. 194-97.

Cooper, J.W. "Adverse Drug Reaction-Related Hospitalizations of Nursing Facility Patients: A 4-Year Study." Southern Medical Journal, Vol. 92 (1999), pp. 485-90.

Corr, K., and R. Stoller. "Adverse Drug Event Reporting at Veterans Affairs Facilities (Letter)." American Journal of Health-System Pharmacy, Vol. 53 (1996), pp. 314-15.

Cullen, D.J., and others. "The Incident Reporting System Does Not Detect Adverse Drug Events: A Problem for Quality Improvement." Joint Commission Journal on Quality Improvement, Vol. 21, No. 10 (Oct. 1995), pp. 541-48.

Cullen, D.J., and others. "Preventable Adverse Drug Events in Hospitalized Patients: A Comparative Study of Intensive Care and General Care Units." Critical Care Medicine, Vol. 25, No. 8 (1997), pp. 1289-97.

Dahlgren, A.F. "Adverse Drug Reactions in Home Care Patients Receiving Nafcillin or Oxacillin." American Journal of Health-System Pharmacy, Vol. 54 (1997), pp. 1176-79.

Dalton-Bunnow, M.F., and F.J. Halvachs. "Computer-Assisted Use of Tracer Antidote Drugs to Increase Detection of Adverse Drug Reactions: A Retrospective and Concurrent Trial." Hospital Pharmacy, Vol. 28 (1993), pp. 746-55.

Dennehy, C.E., and others. "Drug-Related Illness in Emergency Department Patients." American Journal of Health-System Pharmacy, Vol. 53 (1996), pp. 1422-26.

Echt, D.S., and others. "Mortality and Morbidity in Patients Receiving Encainide, Flecainide, or Placebo." New England Journal of Medicine, Vol. 324, No. 12 (1991), pp. 781-88.

Einarson, Thomas R. "Drug-related Hospital Admissions." Annals of Pharmacotherapy, Vol. 27 (1993), pp. 832-40.

Evans, R.S., and others. “Prevention of Adverse Drug Events through Computerized Surveillance.” Sixteenth Annual Symposium on Computer Applications in Medical Care. New York: McGraw-Hill, 1993. Pp. 437-41.

Evans, R.S., and others. “Preventing Adverse Drug Events in Hospitalized Patients.” The Annals of Pharmacotherapy, Vol. 28 (1994a), pp, 523-27.

Evans, R.S., and others. “Using a Hospital Information System to Assess the Effects of Adverse Drug Events.” Seventeenth Annual Symposium on Computer Applications in Medical Care. New York: McGraw-Hill, 1994b. Pp. 161-65.

Faich, G.A. “Adverse-Drug-Reaction Monitoring.” New England Journal of Medicine, Vol. 314, No. 24 (1986), pp. 1589-92.

Flynn, E.A., R.E. Pearson, and K.N. Barker. “Observational Study of Accuracy in Compounding I.V. Admixtures at Five Hospitals.” American Journal of Health-System Pharmacy, Vol. 54 (1997), pp. 904-12.

Folli, H.L., and others. “Medication Error Prevention by Clinical Pharmacists in Two Children’s Hospitals.” Pediatrics, Vol. 79, No. 5 (May 1987), pp. 718-22.

Fremont-Smith, K. “Adverse Drug Reactions in Hospitalized Patients (Letter).” Journal of the American Medical Association, Vol. 280, No. 20 (1998), p. 1741.

Gerety, M.B., and others. “Adverse Events Related to Drugs and Drug Withdrawal in Nursing Home Residents.” Journal of the American Geriatric Society, Vol. 41 (1993), pp. 1326-32.

Goldman, S.A., and others. The Clinical Impact of Adverse Event Reporting. Washington, D.C.: FDA, Center for Drug Evaluation and Research, Oct. 1996.

Gray, S.L., and others. “Adverse Drug Events in Hospitalized Elderly.” Journal of Gerontology: Medical Sciences, Vol. 53A, No. 1 (1998), pp. M59-M63.

Grymonpre, R.E., and others. “Drug-Associated Hospital Admissions in Older Medical Patients.” Journal of the American Geriatrics Society, Vol. 36 (1988), pp. 1092-98.

Gurwitz, J.H., and J. Avorn. "The Ambiguous Relation Between Aging and Adverse Drug Reactions." Annals of Internal Medicine, Vol. 114, No. 11 (1991), pp. 956-66.

Ives, T.J., and others. "Drug-Related Admissions to a Family Medicine Inpatient Service." Archives of Internal Medicine, Vol. 147 (1987), pp. 1117-20.

Jick, H. "Boston Collaborative Drug Surveillance Program." Hospital Pharmacy, Vol. 27, No. 4S (Apr. 1992), pp. S3-S55.

Johnson, J.A., and others. "Drug-Related Morbidity and Mortality: A Cost-of-Illness Model." Archives of Internal Medicine, Vol. 155 (1995), pp. 1949-56.

Johnson, J.A., and others. "Drug-Related Morbidity and Mortality and the Economic Impact of Pharmaceutical Care." American Journal of Health-System Pharmacy, Vol. 54 (1997), pp. 554-58.

Kimmel, S.E., and others. "Adverse Events After Protamine Administration in Patients Undergoing Cardiopulmonary Bypass: Risks and Predictors of Under-Reporting." Journal of Clinical Epidemiology, Vol. 51, No. 1 (1998), pp. 1-10.

Klein, L.E., and others. "Medication Problems Among Outpatients: A Study with Emphasis on the Elderly." Archives of Internal Medicine, Vol. 144 (June 1984), pp. 1185-88.

Lakshmanan, M.C., and others. "Hospital Admissions Caused by Iatrogenic Disease." Archives of Internal Medicine, Vol. 146 (1986), pp. 1931-34.

Lazarou, J., B. Pomeranz, B., and P. Corey. "Incidence of Adverse Drug Reactions in Hospitalized Patients: A Meta-analysis of Prospective Studies." Journal of the American Medical Association, Vol. 279, No. 15 (1998a), pp. 1200-05.

Lazarou, J., B. Pomeranz, and P. Corey. "Adverse Drug Reactions in Hospitalized Patients (Response)." Journal of the American Medical Association, Vol. 280, No. 20 (1998b), p. 1743.

Leape, L.L. "Error in Medicine." Journal of the American Medical Association, Vol. 272, No. 23 (1994), pp. 1851-57.

Leape, L.L., and others. "The Nature of Adverse Events in Hospitalized Patients: Results of the Harvard Medical Practice Study II." New England Journal of Medicine, Vol. 324, No. 6 (1991), pp. 377-84.

Leape, L.L., and others. "Preventing Medical Injury." Quality Review Bulletin, Vol. 19 (1993), pp. 144-49.

Leape, L.L., and others. "Systems Analysis of Adverse Drug Events." Journal of the American Medical Association, Vol. 274, No. 1 (1995), pp. 35-43.

Lesar, T.S., and others. "Medication Prescribing Errors in a Teaching Hospital." Journal of the American Medical Association, Vol. 263 (1990), pp. 2329-34.

Lesar, T.S., and others. "Factors Related to Errors in Medication Prescribing." Journal of the American Medical Association, Vol. 277, No. 4 (1997), pp. 312-17.

Martin, R.M., and others. "Age and Sex Distribution of Suspected Adverse Drug Reactions to Newly Marketed Drugs in General Practice in England: Analysis of 48 Cohort Studies." British Journal of Clinical Pharmacology, Vol. 46 (1998), pp. 505-11.

Mitchell, A.A., and others. "Adverse Drug Reactions in Children Leading to Hospital Admission." Pediatrics, Vol. 82 (1988), pp. 24-29.

Nelson, K.M., and R.L. Talbert. "Drug-Related Hospital Admissions." Pharmacotherapy, Vol. 16 (1996), pp. 701-07.

Orsini, M.J., and others. "An ADR Surveillance Program: Increasing Quality, Number of Incidence Reports." Formulary, Vol. 30 (1995), pp. 454-61.

Pearson, T.F., and others. "Factors Associated with Preventable Adverse Drug Reactions." American Journal of Hospital Pharmacy, Vol. 51 (1994), pp. 2268-72.

Phillips, D.P., N. Christenfeld, and L.M. Glynn. "Increase in U.S. Medication-Error Deaths Between 1983 and 1993." The Lancet, Vol. 351 (1998), pp. 643-44.

Pitt, B., and others. "The Effect of Spironolactone on Morbidity and Mortality in Patients with Severe Heart Failure." New England Journal of Medicine, Vol. 341, No. 10 (1999), pp. 709-17.

Prince, B.S., and others. "Drug-Related Emergency Department Visits and Hospital Admissions." American Journal of Hospital Pharmacy, Vol. 49 (1992), pp. 1696-1700.

Raju, T.N.K., and others. "Medication Errors in Neonatal and Paediatric Intensive-Care Units." The Lancet, Vol. 2 (1989), pp. 374-76.

Raschke, R.A., and others. "A Computer Alert System to Prevent Injury From Adverse Drug Events." Journal of the American Medical Association, Vol. 280, No. 15 (1998), pp. 1317-20.

Rupp, M.T., M. DeYoung, and S.W. Schondelmeyer. "Prescribing Problems and Pharmacist Interventions in Community Practice." Medical Care, Vol. 30 (1992), pp. 926-40.

Salem, R.B., T.M. Keane, and J.G. Williams. "Drug-Related Admissions to a Veterans' Administration Psychiatric Unit." Drug Intelligence and Clinical Pharmacy, Vol. 18 (1984), pp. 74-76.

Saltiel, E., E. Johnson, and R. Shane. "A Team Approach to Adverse Drug Reaction Surveillance: Success at a Tertiary Care Hospital." Hospital Formulary, Vol. 30 (1995), pp. 226-32.

Schneider, J.K., L.C. Mion, and J.D. Frengley. "Adverse Drug Reactions in an Elderly Outpatient Population." American Journal of Hospital Pharmacy, Vol. 49 (1992), pp. 90-96.

Schneider, P.J., and others. "Cost of Medication-Related Problems at a University Hospital." American Journal of Health-System Pharmacy, Vol. 52 (1995), pp. 2415-18.

Schernitski, P., and others. "Demographic Characteristics of Elderly Drug Overdose Patients Admitted to a Hospital Emergency Department." Journal of the American Geriatrics Society, Vol. 28 (1980), pp. 544-46.

Schneitman-McIntire, O., and others. "Medication Misadventures Resulting in Emergency Department Visits at an HMO Medical Center." American Journal of Health-System Pharmacy, Vol. 53 (1996), pp. 1416-22.

Seeger, J.D., and others. "Characteristics Associated with Ability to Prevent Adverse Drug Reactions in Hospitalized Patients." Pharmacotherapy, Vol. 18, No. 6 (1998), pp. 1284-89.

Shaughnessy, A.F., and R.O. Nickel. "Prescription-Writing Patterns and Errors in a Family Medicine Residency Program." The Journal of Family Practice, Vol. 29 (1989), pp. 290-95.

Smith, K.M., and others. "Drug-Related Problems in Emergency Department Patients." American Journal of Health-System Pharmacy, Vol. 54 (1997), pp. 295-98.

Steel, K., and others. "Iatrogenic Illness on a General Medical Service at a University Hospital." New England Journal of Medicine, Vol. 304 (1981), pp. 638-42.

Stewart, R.B., and others. "Drug-related Admissions to an Inpatient Psychiatric Unit." American Journal of Psychiatry, Vol. 137 (1980), pp. 1093-95.

Stoukides, C.A., P.R. D'Agostino, and M.B. Kaufman. "Adverse Drug Reaction Surveillance in an Emergency Room." American Society of Hospital Pharmacy, Vol. 50 (1993), pp. 712-14.

Sullivan, S.D., D.H. Kreling, and T.K. Hazlet. "Noncompliance with Medication Regimens and Subsequent Hospitalizations: A Literature Analysis and Cost of Hospitalization Estimate." Journal of Research in Pharmaceutical Economics, Vol. 2 (1990), pp. 19-33.

Thomas, E.J., and others. "Costs of Medical Injuries in Utah and Colorado." Inquiry, Vol. 36 (Fall 1999), pp. 255-64.

Thomas, E.J., and others. "Incidence and Types of Adverse Events and Negligent Care in Utah and Colorado." Medical Care, forthcoming.

Warren, J.L., and others. "Hospitalizations With Adverse Events Caused by Digitalis Therapy Among Elderly Medicare Beneficiaries." Archives of Internal Medicine, Vol. 154 (1994), pp. 1482-87.

Wolfe, M.M., and others. “Gastrointestinal Toxicity of Nonsteroidal Antiinflammatory Drugs.” New England Journal of Medicine, Vol. 340, No. 24 (1999), pp. 1888-99.

Ordering Information

The first copy of each GAO report and testimony is free. Additional copies are $2 each. Orders should be sent to the following address, accompanied by a check or money order made out to the Superintendent of Documents, when necessary. VISA and MasterCard credit cards are accepted, also. Orders for 100 or more copies to be mailed to a single address are discounted 25 percent.

Orders by mail:

U.S. General Accounting Office
P.O. Box 37050
Washington, DC 20013

or visit:

Room 1100
700 4th St. NW (corner of 4th and G Sts. NW)
U.S. General Accounting Office
Washington, DC

Orders may also be placed by calling (202) 512-6000 or by using fax number (202) 512-6061, or TDD (202) 512-2537.

Each day, GAO issues a list of newly available reports and testimony. To receive facsimile copies of the daily list or any list from the past 30 days, please call (202) 512-6000 using a touchtone phone. A recorded menu will provide information on how to obtain these lists.

For information on how to access GAO reports on the INTERNET, send an e-mail message with "info" in the body to:

info@www.gao.gov

or visit GAO's World Wide Web Home Page at:

http://www.gao.gov

United States
General Accounting Office
Washington, D.C. 20548-0001

Bulk Rate
Postage & Fees Paid
GAO
Permit No. G100

Official Business
Penalty for Private Use $300

Address Correction Requested