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Testimony

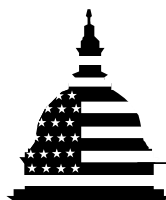
Before the Committee on Health, Education, Labor, and Pensions, U.S. Senate

For Release on Delivery
Expected at 10:00 a.m.
Tuesday, Feb. 1, 2000

ADVERSE DRUG EVENTS

**Substantial Problem but
Magnitude Uncertain**

Statement of Janet Heinrich, Associate Director
Health Financing and Public Health Issues
Health and Human Services Division



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Adverse Drug Events: Substantial Problem but Magnitude Uncertain

Mr. Chairman and Members of the Committee:

I am pleased to have the opportunity to testify as the committee considers adverse medical events in the nation's health care system. Today we are releasing a report that synthesizes current research on adverse drug events (ADE).¹ ADEs have received considerable attention recently as a major component of the medical errors associated with all types of medical treatment highlighted in a recent report of the Institute of Medicine.² In our study, we looked only at adverse events related to drugs and events brought about by human error as well as adverse effects from the appropriate use of drugs.

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 ADEs do occur and can lead to hospitalization, disability, or death. Because the use of prescription drugs is so frequent, even a very low rate of ADEs can result in a large number of serious injuries and deaths.

I will summarize the key findings of our report, in which we examined existing research on ADEs. In the report, we (1) described the different types and causes of ADEs, (2) examined the evidence on the overall incidence and cost of ADEs in the United States, and (3) described measures that have been proposed to reduce the number and severity of ADEs.

Adverse events are injuries caused by medical treatment rather than an underlying disease or condition. ADEs are the subset of adverse events stemming from drug therapy. Some adverse drug events arise from previously known or newly detected adverse reactions to drugs, and others result from medication errors committed by health care professionals in prescribing or administering drugs or the patients themselves in taking them.

Sicker patients are more susceptible to suffering negative effects from a single drug. In addition, their need for more intensive treatment, such as taking several drugs simultaneously, may further increase their risk. Most medication errors do not result in an ADE. Nonetheless, an estimated

¹Adverse Drug Events: *The Magnitude of Health Risk Is Uncertain Because of Limited Incidence Data* (GAO/HEHS-00-21, Jan. 18, 2000).

²Institute of Medicine, *To Err Is Human: Building a Safer Health System* (Washington, D.C.: National Academy Press, 1999).

quarter to half of all ADEs among hospital patients result from medication errors. Medication errors most often occur because 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 incidence or cost. Data routinely collected during clinical trials or after drugs are marketed are intended to identify the types of adverse reactions that are associated with particular drugs and do not focus on their frequency. Information on the incidence of ADEs from all drugs is limited to a few research studies. These typically examined the experience of patients in one or two specific institutions—generally hospitals or sometimes nursing homes—leaving the 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 an especially restrictive definition of ADE and found that ADEs occurred at a rate of 0.56 for every 100 patients admitted in Colorado and Utah and 0.72 in New York. Other studies of single hospitals 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.

Patient safety advocates and researchers have suggested a range of measures to decrease the number and severity of ADEs caused by both adverse reactions and medication errors. Improved communication between patients and physicians about the risks and benefits of medications might help prevent serious drug reactions. Similarly, expanding and accelerating research on the safety of drugs already on the market could more quickly detect previously unknown adverse reactions and determine the risk factors that increase their likelihood. Suggestions for reducing medication errors include developing computerized prescribing and dispensing systems, avoiding sound-alike names and look-alike packaging for medications, increasing the role of pharmacists, 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. Yet, 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 adverse drug reactions. 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.

Within the Department of Health and Human Services, the Food and Drug Administration (FDA) decides which drugs to approve 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 does not require that a drug have no adverse side effects in order to be considered safe. Rather, it evaluates safety in terms of balancing the risks of negative side effects against expected therapeutic benefits. 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 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 manufacturers to change its labeling. Such changes may restrict the conditions for which the drug is approved or may require certain safety precautions. However, new information can also point to expanded uses for a drug. New uses of a drug can also reveal previously unsuspected risks. After more than 20 years on the market, fenfluramine, a weight-loss medication, 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 a drug from the market rather than changing the label.

Multiple Factors Contribute to ADE Risks

Both adverse reactions to drugs and the adverse events caused by human error are more or less likely, depending on the presence of identified risk factors. With respect to adverse reactions, many are the predictable result of a drug's known pharmacological properties and are often listed on the

label. For example, hemorrhaging is the most common adverse reaction for warfarin, a drug that reduces the risk of heart attack, stroke, and other conditions by decreasing the clotting ability of blood. Other adverse reactions, including allergic reactions, are less predictable, caused by sensitivities in individual patients who have no history of adverse reactions to a specific drug. Still other adverse reactions are related to previously undetected risks. These include 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, as well as 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 adverse reactions. Some drug classes are associated with a substantial number of adverse reactions, mainly 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 nonsteroidal anti-inflammatory drugs (NSAIDs). However, some classes of drugs have notably lower rates of adverse reactions despite high rates of use. Antihistamines and the statin drugs prescribed to lower cholesterol levels are rarely associated with serious adverse reactions.

Patients who are very ill, including those with several concurrent diagnoses, have a greater risk of adverse reaction 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. Some reports have found that elderly persons and women have more adverse reactions than younger persons and men. However, it is possible that age and gender are merely related to other risk factors instead of independently increasing the likelihood of an adverse reaction. In some studies, controlling for the number of medications being taken substantially diminishes any relationship between age and adverse reactions.

Of the many medication errors that occur, only a small proportion cause ADEs, either because errors are caught before the drugs are administered or because patients suffered no ill effects despite the errors. Still, an estimated quarter to half of all ADEs among hospital patients result from medication errors. 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.

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 to patients with documented allergies, and prescribing drugs known to interact adversely with other medications patients are taking. Administration errors include giving drugs other than those prescribed, giving drugs at the incorrect time, miscalculating the prescribed dosage, and giving patients the incorrect form of a drug, such as an injection rather than a tablet.

Patients' noncompliance or failure to take drugs as prescribed is also a major source of error. Outside the hospital and other health care institutions, patients are responsible for taking medications as directed. They may underuse or overuse drugs, prematurely discontinue medications, or take medications inconsistently. Their noncompliance is an important cause of emergency department visits and hospital admissions.

Analgesics, antibiotics, and cardiovascular and psychotropic drugs are among the classes of drugs consistently associated with medication errors. Some drugs are inherently risky. For example, drugs such as the anticoagulant warfarin and the cardiac stimulant digoxin have narrow therapeutic indexes, which means that a slightly incorrect dose can result in serious adverse events. Other drugs involve much less risk to an individual, but so many people take them that many ADEs occur.

Medication errors can occur when different drugs have similar names. 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. Their names look and sound alike but they represent very different drugs—a pain medication used to treat arthritis, an antidepressant, and an antiseizure drug, respectively.

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 and cost of ADEs across the range of medications prescribed and the settings where patients receive treatment.

ADEs must be identified before they can be counted. Frequently this is not a straightforward task. Linking a particular symptom to a specific drug can be 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. Sometimes ADEs can be extraordinarily difficult to detect, such as when symptoms develop only with the prolonged use of a drug or when adverse symptoms mimic those of a patient's underlying condition.

Safety is a prominent concern throughout drug development. Many dangerous substances are identified during this process and their testing is then halted. Nonetheless, by themselves, the results of clinical trials submitted to FDA cannot provide comprehensive information on possible adverse events. First, the number of patients typically included in clinical trials before a drug is approved, generally about 4,000, is too small to detect less frequent adverse events. Consequently, adverse events that occur in 1 of 10,000 patients 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 identified.

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 true incidence. 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. Experts believe that FDA's system includes an estimated 1 to 10 percent of adverse reactions.

In addition, the adverse events that are reported are unlikely to represent 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. Consequently, any estimate of ADE incidence based on a spontaneous reporting system such as AERS would necessarily incorporate the biases of the data, underrepresenting some types of adverse events and overrepresenting others. FDA recognizes the limitations of its spontaneous reporting system. It therefore augments the data in AERS with information from other sources, including analyses of

medical and pharmaceutical records maintained by several large health maintenance organizations.

The data collected routinely before and after drug approval relate to specific medications. Only a limited number of research studies have examined the frequency of ADEs across a broad spectrum of medications. The large majority of these studies deal exclusively with patients treated in hospitals. There are few studies of ADEs among nursing home residents and fewer still of ADEs in the community. The general lack of information about the incidence of ADEs outside hospitals and nursing homes means that estimates of overall ADE incidence based on current knowledge are necessarily limited to these institutional settings.

Among the existing studies, all but a few analyze data from just one or two specific hospitals or nursing homes. This limits the ability to generalize from their results to other comparable institutions. 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 rate of ADEs.

Two studies with statewide samples of patients, but a restrictive definition of ADEs, found rates of 0.56 and 0.72 ADEs for every 100 hospital admissions. Only ADEs that resulted in disability, prolongation of a patient's hospital stay, or death were counted, meaning that a significant fraction of the patients injured by drugs was omitted. The studies included a representative sample of all nonpsychiatric patients treated in acute care hospitals in New York in 1984 and a comparable sample of 1992 hospital discharges in Colorado and Utah.³ The databases for these studies are far more diversified and representative than those of the other studies we examined. The similarity of the rates of ADEs found in these two studies, despite the differences in time and place, suggests that regional and temporal variation in ADE incidence may not be very large.

Other studies of ADEs among patients in individual hospitals have employed highly variable but generally more expansive definitions of ADEs. They reported ADE incidence rates ranging from 2.0 to 30 ADEs per 100 admissions.

Identified studies of ADE incidence in nursing homes examined only one or two institutions. As with the hospital studies, the definition of what

³T.A. Brennan 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, and E.J. Thomas and others, "Incidence and Types of Adverse Events and Negligent Care in Utah and Colorado," *Medical Care*, forthcoming.

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 much broader definition.⁴ These rates are roughly comparable with the rate reported by the one study of hospital ADEs that presented ADE incidence in terms of time spent in the hospital.⁵

Data on mortality from ADEs are even more sparse than the data on ADE incidence. Recently, Lazarou, Pomeranz, and Corey attempted to synthesize available data on fatalities from adverse drug events (excluding cases of medication error).⁶ To derive their estimate of 106,000 fatal adverse drug reactions in the United States in 1994, they drew on data from 16 studies of adverse drug reactions published between 1964 and 1995. The studies cumulatively looked at 78 deaths, but only two of the studies had more than 10 deaths. Moreover, the 4 studies published after 1976 included a total of 5 deaths, compared with 73 in the 12 earlier studies. Consequently, the projection of fatal adverse drug reactions in 1994 was based predominately on data from 20 years earlier, when the use of pharmaceuticals was quite different. In addition, deaths were too few to arrive at a stable mortality estimate—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.

The paucity of incidence data for ADEs in the United States has also impeded efforts to estimate their nationwide costs. Researchers have followed different approaches in attempting to generate some information about the costs of treating ADEs. Some have extrapolated from the experience of individual hospitals. Others have turned to expert panels to estimate the likely probability of specific adverse outcomes and associated costs for hospital patients and nursing home residents. The results obtained in each of these approaches depends on the specific hospital or experts included in the study.

⁴M.B. Gerety 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, and J.W. Cooper, "Drug-Related Problems in a Geriatric Long Term Care Facility," *Journal of Geriatric Drug Therapy*, Vol. 1 (1986), pp. 47-68.

⁵D.W. Bates 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 (1995), pp. 29-34.

⁶J. Lazarou, B. Pomeranz, 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 (1998), pp. 1200-05.

The most extensive data available on ADE costs come from the 1999 study of adverse events in Colorado and Utah that I previously described.⁷ 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 patients' 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 estimate for hospital costs alone was \$5.2 billion. 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 other studies of ADE costs, although it is still limited to Colorado and Utah. In extrapolating their results to an aggregate national estimate, the authors did not attempt to adjust for the likely variation in hospital admission rates, hospital costs, and personal incomes in other parts of the country.

Variety of Measures Proposed to Reduce the Number and Severity of Adverse Drug Events

Patient safety advocates and researchers have identified factors and proposed measures that they believe could reduce both adverse drug reactions and ADEs caused by medication errors.

The process of drug research and development itself could help reduce adverse reactions 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 and ibuprofen. Moreover, expanding physician education—and communication between physicians and patients—about the benefits and risks of particular drugs could promote more informed decisionmaking about pharmaceuticals and thereby help reduce the incidence of adverse reactions. Given the large number of drugs on the market and the voluminous information about each one, 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.

⁷E.J. Thomas and others, "Costs of Medical Injuries in Utah and Colorado," *Inquiry*, Vol. 36 (Fall 1999), pp. 255-64.

Expanded surveillance programs to gather information about marketed drugs might also help prevent adverse reactions 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. More extensive incidence data about the specific risks associated with new drugs could assist physicians and patients to make more informed treatment choices.

With respect to reducing medication errors, numerous measures have been taken and experts have proposed others to make it more difficult for errors to occur 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 applicable to both drug manufacturers and health care providers.

**Adverse Drug Events: Substantial Problem
but Magnitude Uncertain**

Table 1: Current and Proposed Approaches to Reduce Medication Errors

	Intended benefit
Dispensing change	
Physicians' direct computer entry of prescriptions	Physicians' entering prescriptions on a computer rather than writing them reduces transcription errors and potentially indicates 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.

Conclusion

The existing research on adverse drug events makes clear that many patients experience negative outcomes from drug therapy. These derive from both adverse reactions to the inherent pharmacological properties of drugs given appropriately and from mistakes made by health care professionals and patients themselves. Researchers have identified several risk factors that make it more likely that patients will experience ADEs.

However, there is little precise information about the rate at which ADEs occur and their costs. Most of what is known on incidence and costs is highly fragmentary, relating to specific drugs or specific institutions. Information on ADEs outside hospitals or nursing homes is especially sparse. A variety of measures have been proposed to reduce the number and severity of adverse drug reactions and medication errors leading to ADEs. Our work in this area will continue as we proceed to examine the existing system of postmarketing surveillance in the United States and to consider possible changes to improve its effectiveness.

This concludes my prepared statement, Mr. Chairman. I will be happy to respond to any questions that you or members of the committee may have.

Contacts and Acknowledgments

For future contacts regarding this testimony, please call Janet Heinrich at (202) 512-7119. Key contributors include Robert M. Copeland, Martin T. Gahart, Eric A. Peterson, and Helene F. Toiv.

(201025)