

SPECIAL ARTICLE

Can the Frequency and Risks of Fatal Adverse Drug Events Be Determined?

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Death is the ultimate adverse drug event. Despite its importance, the frequency of fatal adverse drug events is unknown. Estimates in the United States are as high as 140,000/year, although this number is heavily disputed. Potential reasons and risks for fatal adverse drug events, as well as epidemiologic designs for studying this important public health issue, are discussed and issues are raised to promote further thought.

(*Pharmacotherapy* 2001;21(5):521–527)

Given the number of drugs and doses delivered, drugs are remarkably nontoxic. Fatal adverse drug events (ADEs)—for which there is no standard definition—are estimated to occur in less than 0.01% of people taking drugs.¹ However, when one considers the number of lives that could be saved or if such an event involved a loved one, then this issue immediately becomes more important. For the purposes of this article, a fatal ADE is a death that occurs when a prescribed drug intended for prophylactic, diagnostic, or therapeutic purposes in all likelihood led to death. This definition excludes deaths from intentional suicide by drug ingestion and from drug abuse. Results from a medical inpatient study estimated 140,000 hospital deaths resulting from drug therapy each year in the United States—an extrapolation that has been criticized.^{2,3} Still, based on this estimate, fatal ADEs would be the third leading cause of death in the U.S.

Medical inpatients, who constitute approximately one-third of hospital admissions, receive more drugs and experience the most adverse drug reactions compared with other patient groups. Although the death rate from ADEs is

less than that from diseases of the heart (725,000 deaths/yr) or cancer (542,000 deaths/yr), it may be higher than the death rate from pneumonia and influenza (92,000 deaths/yr).⁴ Although these comparisons are revealing, the annual number of fatal ADEs is an estimate based only on hospitalized patients. The corresponding number in the ambulatory population is unknown.

Etiology

To understand why fatal ADEs occur, the traditional categories of adverse drug effects must be explored. Type A reactions are pharmacologic and dose related; type B are neither pharmacologic nor dose related, and often are unexplainable.

Type A adverse drug reactions that lead to death are usually the result of toxicity, from either error or nonerror causes. Errors that may cause toxicity include prescribing too much of a correct drug (overdose) for the patient's age or weight, prescribing a drug contraindicated for the patient's condition, providing the correct drug by the wrong route or too quickly (e.g., parenteral administration), and drug interactions (as most drug interactions are known, their adverse effects should be classified as preventable errors).

Nonerror causes of toxicity include decreased renal function if the drug is excreted renally, decreased liver function if the liver metabolizes the drug, abnormal hematology, and genetics. However, if abnormal renal or liver function or

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Table 1. Uncontrolled Inpatient Prevalence Studies of Fatal ADEs

Hospitals	Patients	No. of Pts	No of Cases	Prevalence	Period
1 ⁷	Medical	714	6	0.8	3 mo
1 ⁸	Medical	900	2	0.22	1 yr
1 ⁹	Medical	731	17	2.30	1 yr
1 ¹⁰	Medical	939	8	0.85	8 mo
8 ¹¹	Chronic medical	6199	27	0.44	3 mo
1 ¹²	Medical	1239	0	0	3 yrs
9 ¹³	Medical	13,829	33	0.29	6 yrs
1 ¹⁴	Medical	6199	27	0.44	3 mo
21 ¹⁵	Acute medical	26,462	24	0.09	5 yrs
24 ¹⁶	Surgical	10,281	2	0.02	11 mo
2 ¹⁷	Hospitalized	1268	0	0	1 yr
1 ¹⁸	Hospitalized	8291	1	0.01	1 yr
Several ¹⁹	Hospitalized	9104	8	0.09	6 mo
2 ²⁰	Hospitalized	4031	3	0.07	6 mo

abnormal hematology are factors contributing to toxicity, and baseline studies were not performed before the drug was prescribed and/or the drug is known to produce adverse hematologic effects, then these events should be considered errors.

Genetic causes of drug toxicity are now being implicated. For example, patients who are slow metabolizers of drugs degraded by the cytochrome P450 enzyme system may be at risk for serious drug toxicity, even when receiving the correct dosage.⁵

Type B reactions may be immunologic. However, when a patient reports an allergy to a drug and still receives it, the adverse event should be categorized as an error. Because type B reactions are unpredictable, they often are regarded as unpreventable. As the liver, kidney, and blood are most susceptible to adverse drug effects,⁷ baseline laboratory assessments are recommended before prescribing drugs associated with fatal ADEs, which may prevent them from occurring.

In a recent analysis of 447 spontaneous case reports concerning fatal ADEs, 34% were type A and 66% were type B. Mechanisms for fatal ADEs were adverse drug reactions (58%), drug allergies (19%), drug errors (17%); and drug interactions (6%).⁶

Study Limitations

Determining the true frequency of fatal ADEs is difficult, as they are based on self-reporting. Occurrences are often buried in institutional incident reports or are legal settlements shielded from review by outside investigators. Even when cases of fatal ADEs come to light, causality assessment and other important data are often

missing.⁶ In addition, problems arise in deciding the accuracy of the numerator (number of fatal ADEs) and the denominator (number of patients receiving the drug).

Pertinent Studies

In a MEDLINE search using the term "fatal adverse drug reactions," only studies reporting a prevalence rate for drug-induced death were reviewed. The search revealed 14 inpatient studies, two cross-sectional studies, two pathology studies, one death-certificate study, one meta-analysis, and one controlled study. Few of the studies defined a fatal ADE, and many did not provide details on causality assessment or standard deviations on mean prevalence rates.

Inpatient Studies

Nine uncontrolled prevalence studies of fatal ADEs conducted between 1966 and 1977 on medical patients⁷⁻¹⁵ varied in length from 3 months–5 years; the number of hospitals for each study varied from 1–21. Consecutive admissions usually were monitored for adverse drug reactions using various methods of surveillance and causality assessment. The prevalence of fatal ADEs ranged from 0–2.3% of admissions. Inpatient medical units that mostly had patients with chronic diseases had higher prevalence rates than units primarily treating acute ailments. The mean prevalence of fatal ADEs from these nine studies was 0.578%.

The only uncontrolled study that included surgical inpatients¹⁶ revealed a fatal ADE prevalence rate of 0.019% (95% confidence interval [CI] 0.002–0.071%). A higher prevalence rate was found for medical patients,

Table 2. Cross-Section Studies on Fatal ADEs

Data Source	Period	No. of Pts	No. of Cases	% Fatal ADRs
Canadian HPR ^{a, 23}	1984–1994	60,518	1494	2.5
United States FDA ²⁴	1989–1993	421,491	9651	3.2

^aAdverse drug reaction monitoring division of the Health Protection Branch.

but the difference no longer existed after adjusting for the number of drugs taken by these patients.

In three uncontrolled inpatient studies of mixed (medical, surgical, gynecologic, and psychiatric) patient populations,^{17–19} prevalence of fatal ADEs ranged from 0–0.09%. The mean prevalence was 0.03%—a rate that falls between the expectable prevalence for medical and surgical patients based on severity of illness. In one uncontrolled, prospective cohort study,²⁰ the frequency of fatal ADEs was 0.07%.

The only large, controlled study of fatal ADEs in hospitalized patients²¹ consisted of 91,574 patients admitted to one tertiary health care center. Of 2227 patients who developed a fatal ADE, 1580 were matched using the same admission period, age (\pm 10 yrs), discharge diagnosis, and hospital acuity score category with 20,197 controls. The crude mortality rate was 3.5% for study patients versus 1.05 for controls ($p < 0.001$).

Table 1 provides relevant information on the inpatient studies.

Meta-Analysis

One meta-analysis that examined four electronic databases over a 3-year period²² revealed an overall incidence of fatal ADEs in hospital patients of 0.32% (95% CI 0.23–0.41%). The authors estimated that 106,000 (range 76,000–137,000) patients died from ADEs during 1994.

Cross-Sectional Studies

The results of two cross-sectional studies of large U.S. and Canadian government databases on spontaneous adverse drug reactions are summarized in Table 2.^{23, 24} Fatal ADEs represented 2.5–3.2% of all adverse reactions reported.

Pathology Studies

Two postmortem studies from the 1970s on fatal ADEs are summarized in Table 3.^{25, 26} One

Table 3. Pathology Reports on Fatal Adverse Drug Events

No. of Pts Admitted	No. of Deaths	No. (%) of Autopsies	No. (%) of Fatal ADEs
99,029 ²⁵	3077	2168 (70)	179 (0.254) ^a
—	—	—	827 ²⁶

^aAdjusted for percentage of autopsies completed.

study determined that $8.3 \pm 0.6\%$ of deaths of hospitalized patients were drug associated.²⁵ The other study found that 52% of drug-associated deaths involved overdose, 6% malignant conditions treated with cytotoxic drugs, and 3% diagnostic or therapeutic errors. Of the 827 patients who experienced adverse drug reactions (ADRs) in whom autopsies were done, 25% of the cases met the strict criteria of ADRs and were also lethal.²⁶ However, both pathology studies may have included cases of drug abuse. With the decline in autopsy rates, such studies are unlikely to be reported in the future.

Death Certificate Study

A study of death certificates from 1983–1993 revealed an increase in drug-error deaths from 2876 to 7000/year in the U.S., a 2.57-fold increase.²⁷ This prevalence does not include other causes of fatal ADEs such as adverse reactions. However, the limitations of using death certificates are well known.²⁸ Death certificate diagnoses are usually clinical diagnoses and are subject to all of the vagaries of this description. In addition, several diseases may have contributed to a patient’s death, but under current procedures, only one underlying cause of death can be listed.

Ambulatory and General Population Studies

What is the true prevalence—that is, death from taking at least one dose of a causal drug—for fatal ADEs? The mean prevalence for all the inpatient studies is 0.385%. The prevalence of fatal ADEs in the general population remains elusive but is expected to be much lower than that in hospitalized patients.

Danger of Extrapolations

Extrapolations based on sparse and inadequate data concerning fatal ADEs are dangerous; those based on medical inpatient studies only are of doubtful validity and have been severely criticized. Further, although using mean prevalence rates, or attempting a meta-analysis of various patient populations might be more accurate, these approaches remain inappropriate for several reasons. First, study methods vary from study to study. Second, some studies do not define fatal ADEs, and when the term is defined, definitions vary among studies. Third, the prevalence or incidence rate for fatal ADEs in the ambulatory population is not known.

The U.S. Institute of Medicine recently stated that as many as 98,000 people in U.S. hospitals die each year because of medical errors,²⁹ a proportion of which are fatal ADEs. The methods used to produce the Institute of Medicine's estimate remain questionable,³⁰ as the actual annual number of fatal ADEs in U.S. hospitals and in the ambulatory environment may be much higher or lower than this estimate.

Reasons To Study Fatal ADEs

Although the frequency of fatal ADEs is relatively low, reasons to study this unwanted outcome of drug therapy are compelling. Loss of life from ADEs is both tragic and often avoidable. One descriptive study found that 45% of case reports of drug-induced deaths occurred in people aged 40–69 years, of whom 40% were healthy, and 17% of fatal ADEs occurred in children (from birth to 17 yrs old).⁶

Although information on fatal ADE prevention is insufficient, it is possible. Almost all type A reactions can be prevented, and some type B might be minimized by careful baseline assessment. Two studies assessing preventability of fatal ADEs using standardized criteria^{6,7} produced estimates that varied from 25–68% due to differences in criteria.

Developing Prognostic Criteria for High-Risk Patients

The distribution of risk for a major negative outcome (death, a permanent disability, a life-threatening condition) from drugs is uneven across a large population. The combination of high-risk patients and drugs with a low therapeutic index increases the likelihood of fatal ADEs. If the principal risk factors can be

determined, then software can be developed to screen for those who may be at high risk before the drug is prescribed or dispensed. Such screening recently occurred at a large university hospital in St. Louis, Missouri.³¹

Risk Factors

What are the determinants of fatal ADEs? No one knows. In fact, it appears that little work has been done in this area. Death is the ultimate adverse drug outcome. Most of the work on drug causality has been in the “can it,” “will it,” and “did it” domains.³² More work is needed beyond exposure and causality in the “why did it?” and the “how can it be prevented?” domains.

A controlled study in hospitalized patients showed that ADEs occur more often in sicker patients who stayed in the hospital longer. After adjusting for level of care and pre-event length of stay, no risk factors remained. However, the study only looked at ADEs in general, not fatal ADEs alone. In addition, only a limited number of risk variables were analyzed.³³

Several patient and drug variables require study to determine if they are risk factors for fatal ADEs; some may be implicated heavily while others may not. For example, the inherent toxicity of the drug is known³⁴; in contrast, age is suspect.^{35,36}

Potential patient risk variables for fatal ADEs include severity of illness, history of allergy, history of ADEs, impaired renal or liver function, age, information from complete blood work-up, comorbidity, history of alcohol or substance abuse, gender, race, obesity, smoking, and genetic profile. Drug risk variables might include inherent toxicity of the drug, dosage, route of administration, duration of therapy, and number of concomitant drugs.

Key Issues in Studying Therapy-Associated Death

In order to ascertain the prevalence of fatal ADEs in the general population, major determinants must be identified and quantified for how strongly they are associated with the outcome. Some reasons why these basic factors for study have not been addressed in any controlled fashion follow.

Ascertaining Cases

The first problem, and perhaps the most difficult, is finding cases. Fatal ADEs, compared with other ADEs, are relatively rare. A second

Table 4. Fatal ADE Protocol Issues, Problems, and Data Source

Protocol Issue or Problem	Vital Statistics,		Large
	Death Certificates	Hospital Records	Population Database
Case identification	±	-	-
Exposure specificity	-	+	-
Causality specificity	±	-	-
Generalize to population	+	-	+
Sufficient sample size	±	-	+
Availability of all variables	-	+	±

+ = favorable, - = unfavorable, ± = neutral.

problem is that the cases are probably not properly described in medical records, databases, and death certificates, for which there are at least three major reasons. First, although a drug may be the major factor in contributing to a death, the actual cause of death is usually recorded by physicians in biological terms on death certificates (e.g., respiratory depression, cardiac arrest). Second, few physicians feel comfortable incriminating a drug that they were responsible for prescribing and monitoring, a medicolegal reason. Third, causality is difficult to assess.

Assessing Causality

Distinguishing in a single case whether the drug, the disease process, or some other circumstance led to a patient’s demise is often difficult. Most physicians are not well trained in assessing causality. Even pharmacoepidemiologists using global introspection often disagree. Other methods of causality assessment, such as the use of algorithms and Bayesian techniques, may be more accurate. However, these methods are difficult and take longer to use.³⁷

Because of the difficulty in establishing causality and the uneasiness in calling a fatal ADE a fatal ADE, cases are difficult to locate and therefore gross underreporting occurs. Causality assessment is important in performing large, linked database studies. As a minimum, the death should be consistent with the actions of the drug. However, using this as a sole criterion eliminates type B fatal ADEs. Sources for cases can be death certificates, medical record review, and database coding. After each source is investigated to see which is best suited for studying fatal ADEs and a source is chosen, all cases will require validation for exposure and then be carefully assessed for causality.

Exposure, Hazard Function, Time Window, and Population

All salient variables relate to the following questions: Did the patient receive the drug? When was the drug started? Was it immediately before the death? How long did the patient receive it? At what point within the drug’s hazard function—its risk over time (a function of inherent toxicity, not exposure)—did the patient die? Because each drug has its own hazard function, matching controls for each drug may be needed. Exposure also requires a similar tracking procedure for controls.

Obtaining a study population to answer the research questions may not be easy, and the importance of focusing on the general public compounds the problem, as does the bias associated with gathering information from the family of the deceased. Table 4 summarizes some of the key issues in designing a study appropriate for answering the research questions. To design a properly controlled epidemiologic study, several sources of information may be needed. This, too, can be problematic, as use of several information sources may seriously weaken the ability to generalize results.

Explanatory Variables

In identifying the risks for fatal ADEs, recording an extensive list of explanatory and descriptive variables for each case is necessary, and large population databases usually do not contain all the necessary information. Medical records contain most information, but review of individual patient records is very time consuming and expensive to abstract. Prospective data collection is best, but also very expensive and time consuming.

Feasibility

Regardless of the difficulties inherent in this type of investigation, several research questions are pertinent:

1. What is the prevalence and incidence of drug-associated death in the general population?
2. What is the relative risk of an individual dying from the legitimate use of a drug?
3. What are the primary risk factors for fatal ADEs?

At least two designs may adequately answer these questions. When the outcome is rare, the nested case-control and case-cohort designs can provide economic estimates of relative risk while requiring exposure and covariate information on a small subset of the cohort.³⁸

Case-Cohort Design

This design could provide the incidence and relative risk of fatal ADEs but does not address the need for data in the general population.³⁹ Because fatal ADEs are so rare, accumulating cases would take a long time and would be costly, even if the same controls were reused until they conformed to the parameters established to constitute one case. Focusing on a component of the problem might be accomplished by stopping after a certain number of cases (e.g., 1000) of confirmed fatal ADEs using a causality algorithm, with three or four controls (surviving patients) randomly selected for each case. Explanatory variables would be collected prospectively.

Nested Case-Control Design

This design would be more cost-effective and less time-consuming than the case-cohort design.⁴⁰ A large series of confirmed cases of fatal ADEs could be identified; finding cases and controls should not be difficult. Medical records can be used to validate computer records and to collect variables not already in the database. The problems with this design lie in determining prevalence and being able to generalize results. If needed, the size of the project could be limited to cases in which drugs cause more than a certain number of deaths, although this is not ideal.

Limitations

With each of these suggested study designs, sensitivity to subtle issues may be difficult. For example, the frequency of fatal ADEs reflects prescribing habits that vary considerably from one geographic area or even one prescriber to another.⁴¹ Frequency also may vary according to the underlying illness (e.g., cancer, terminal liver disease), its severity, and the drugs used to treat it (confounding by indication).

Summary

Several aspects of fatal ADEs reveal its elusive prevalence and incidence in the general population, its probable etiology, reasons for study, and its potential risk factors. Several aspects regarding the design of sound epidemiologic studies to help answer some unresolved questions about this malady have been identified.

The relatively rare prevalence and incidence of fatal ADEs should not preclude study. This is attested to by increasing evidence that suggests that fatal ADEs may be one of the leading causes of accidental death in the U.S. as well as mounting public awareness of the problem.^{42, 43} Strong indicators point to the demand for more recognition and study of, as well as proactive response to, fatal ADEs.

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