

ADVERSE DRUG REACTIONS

Medical and Legal Considerations

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The people of the United States are enamored with drugs. They consume between 2 and 10 times more prescription and over-the-counter drugs than any comparable population anywhere in the world.⁴⁰ The average hospitalized patient is prescribed between 6 and 13 drugs,¹⁵ and the country's aging population is frequently treated with multiple medications for a variety of ailments.⁵ More than 1.6 billion prescriptions for some 30,000 different drugs are written each year in the United States.¹⁷ Approximately 200 new pharmaceuticals are approved annually by the Food and Drug Administration (FDA). This figure does not include consumption of the more than 450 herbal products on the market today (i.e., approximately 8 to 10 billion herbal capsules are produced on a daily basis). Americans are spending more than \$3 billion a year on herbal products, and their popularity has grown faster than American scientists can research them or the FDA can regulate them.

The goal of physician-prescribed medication is to achieve an optimal therapeutic outcome. This goal has been defined as "the right drug for the right patient at the right time."¹⁰ An optimal therapeutic outcome also implies the absence of any drug-related problems.²¹ The latter is defined as an event or circumstance involving a patient's medications that actually or potentially interferes with the achievement of an optimal outcome.²¹ It goes without saying that drug-related problems are frequent outcomes of medical management because medications are dispensed by an imperfect process, and few available therapeutic agents have no undesirable effects. Seven general categories of drug-related problems have been identified⁴³:

- Failure to start a drug for an indicated medical problem
- Administration of a drug in the absence of a valid indication
- Administration of an inappropriate drug for an indicated medical problem

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- Development of a de novo medical problem or worsening of an existent health problem because of a failure to administer an indicated drug
- Administration of an ineffective dose of an appropriate drug
- Administration of an overdose of an appropriate drug
- Undesirable or unexpected effect of an appropriate drug

This article focuses on the issues principally related to adverse drug reactions and their potential medical and legal implications.

EPIDEMIOLOGY, INCIDENCE, AND ECONOMIC IMPACT OF ADVERSE DRUG REACTIONS

The dispensation of pharmaceuticals is the most common therapeutic intervention in any physician-patient encounter. Because there is an absence of mandatory reporting of adverse drug reactions in this country, there is no way to know precisely what percentage of consumed pharmaceuticals produce adverse side effects.^{17, 40} The estimates of significant side effects range from the tens of thousands to several million per year.

An increasing number of studies have addressed the incidence and economic impact of adverse drug reactions. The University of Florida reported that 2.9% of admissions to a medical service were caused by drug-related illness, and more than 6% of these patients died. They further reported that 82% of these reactions involved prescription medications.¹² The Boston Collaborative Drug Surveillance Project estimated that approximately 30% of hospitalized patients experience adverse events attributable to drugs, and that from 3% to 28% of all hospital admissions are related to adverse drug reactions.²³ Further, adverse drug reactions are expected in about 0.31% of hospitalized patients in the United States.^{25, 32} Shapiro et al⁴² summarized a variety of reports of estimated hospital deaths from adverse drug reactions and found a range of 1% to 2.3%. The Boston Collaborative Surveillance Study estimated that 0.9 patients per 1000 inpatients died as a result of an adverse drug reaction.³⁸

In the late 1950s, Congress established the FDA in the wake of the unfortunate circumstances related to the chloramphenicol-induced aplastic anemia cases. The importance of this legislation was born out by the thalidomide catastrophe of 1961, which focused the attention of physicians, the pharmaceutical industry, the public, and the government on the relative safety of drugs on the market. A later revision of the FDA legislation mandated that the pharmaceutical industry report all adverse drug reactions to the FDA. Some of these important early developments related to adverse drug reactions are reviewed by Karch and Lasagna.²⁵

Industry-related reports to the FDA are clearly only a fraction of the total number of adverse events, however. Ninety percent of the total reports come through the manufacturer probably via reports from the physician. Only a small number of adverse drug reactions, especially in ambulatory settings, are voluntarily reported to the FDA by physicians and dentists. These care providers have an innate fear of reporting serious or fatal reactions because of litigation that may be precipitated.⁴⁰ Many physicians are not even aware of the FDA adverse reaction form in the back of the *FDA Drug Bulletin* sent to each physician and dentist several times each year.

The issue of adverse drug reaction reporting is further complicated by the fact that it is often impossible to link a specific symptom complex with a particular drug, especially when this occurs in the setting of a complicated

illness that is being treated with several pharmaceutical agents.¹⁶ Despite these limitations, continuous surveillance has yielded important associations between certain pharmaceuticals and specific adverse reactions.^{14, 15}

The cost of personal prescription medications in the United States was reported to exceed \$77 billion in 1995.²² Johnson and Bootman²⁴ have estimated that the cost of drug-related morbidity and mortality was \$76.6 billion, with the majority (\$47 billion) related to hospital admissions associated with drug therapy or the absence of appropriate drug therapy.²⁴ By comparison, the cost of all diabetes care has been estimated at \$45.2 billion.²⁴

Recent studies have greatly enhanced our insight into the nature, incidence, cost, and possible prevention of adverse drug reactions.^{4, 7, 9, 13, 28, 30, 31} Investigations show that medical therapy results in unintended injuries estimated to affect 1.3 million people each year in the United States.³⁰ Many injuries are unavoidable, but as many as two thirds may be secondary to errors in drug management. Leape^{29, 30} has observed that although human errors result from a number of complex cognitive mechanisms, investigations of major catastrophes such as that at Three Mile Island and the Challenger accident indicate that it is often a series of events set in motion by faulty system design that either induces errors or makes them difficult to detect. Many medical errors result from poor systems design or system failures that have been described as "accidents waiting to happen."^{30, 37} The modern approach to adverse drug events in the practice of medicine has been to focus on the issue of system failures instead of focusing on individuals or specific episodes.^{3, 30} The objective of modern system design is to build in safeguards that make it difficult for individuals to make errors or to absorb errors that do occur (i.e., permit their detection and correction before damage results).^{3, 29, 30}

CLASSIFICATION OF ADVERSE DRUG REACTIONS

There have been a number of different classifications proposed for adverse drug reactions. The classification most frequently cited is that of DeSwarte.¹⁶ He divided adverse drug reactions into *predictable* ones that are generally dose-dependent, related to the pharmacologic action of the drug, and that occur in otherwise normal patients. *Unpredictable* ones are dose-dependent, unrelated to the pharmacologic action of the drug, and tend to occur in susceptible patients. A classification of both types of adverse drug reactions follows^{8, 11, 16, 36}:

- PREDICTABLE
 - Overdosage
 - Side effect
 - Secondary or indirect effect
 - Drug exclusive
 - Drug associated with a disease
 - Drug interactions
- UNPREDICTABLE
 - Intolerance
 - Idiosyncrasy
 - Immunologic (allergic)

The majority of adverse drug reactions are predictable in nature (70% to 80%). Perhaps the most frequent variant of a predictable reaction is the *side effect*, which is defined as a therapeutically undesirable, but often unavoidable, action

of the drug (e.g., sedation associated with first generation H_1 antagonists). The next most frequent type is *overdosage*, which is directly related to the local or systemic concentration of the drug in the body (e.g., seizures associated with theophylline toxicity). *Secondary or indirect effects* may be exclusively related to the drug in question (e.g., diarrhea caused by disruption of bowel flora) or may be related to the drug and an underlying illness (e.g., ampicillin rash in viremia). Finally, drug *interaction* may be beneficial when synergism is desirable (e.g., antimicrobial therapy for tuberculosis) or it may be deleterious in other instances (e.g., aspirin and warfarin).

Unpredictable adverse reactions are less common and more likely to have legal repercussions. *Intolerance* is the unexpected, increased expression of the characteristic pharmacologic effect of a drug (e.g., tinnitus associated with a small dose of aspirin). *Idiosyncrasy* is used to describe a qualitatively abnormal response to a drug that differs from its expected pharmacologic actions. Idiosyncrasy may resemble an allergy or hypersensitivity (e.g., coumadin-induced skin necrosis with protein-C deficiency or the reaction observed in a slow acetylator of isoniazid). *Immunologic (allergic) reactions* are generally rare and unrelated to the pharmacologic reaction of the drug. Unlike idiosyncratic reactions, immunologic drug reactions are the result of an immune response to a drug following a prior exposure to the specific drug, or an immunochemically related substance (e.g., disseminated urticaria and angioedema resulting from repeated sulfa administration). Immunologic (allergic) reactions share a number of the following features in common, which help to identify them^{15, 16, 36}:

- Encountered in only a small number of individuals receiving the drug
- Previous exposure and sensitization to the drug (or chemically related product) is required
- Reactions may be precipitated with very small amounts of the doses well below the therapeutic range
- Reactions are dissimilar to the usual pharmacologic effects of the drug
- Rapid onset of the reaction following administration (5 to 30 minutes)
- Symptom-complex induced resembles other classic allergic reactions (e.g., anaphylaxis, urticaria, and so forth)
- Frequently associated with peripheral or tissue eosinophilia
- Associated with defined biological markers (e.g., specific antibodies)
- Subside within 48 to 72 hours after discontinuing the drug

FACTORS INFLUENCING THE DEVELOPMENT OF ADVERSE DRUG REACTIONS

Several factors assist in predicting whether a given individual will react to a drug. Some are specific to the chemical structure of the drug and its track record. A high-molecular-weight, protein-reactive material is more likely to be associated with sensitization (e.g., insulin, chymopapain, heterologous sera, and so forth), but in the absence of this, certain drugs are quickly metabolized or degraded into reactive moieties (e.g., penicillin). After many years of use, certain classes of drugs are known to be associated with significant allergic reactions (e.g., penicillins and sulfonamides). Other factors that influence immunologic sensitization include cross-sensitization caused by shared antigenicity, route of administration, and degree of exposure. For example, topical drug application is associated with a higher incidence of sensitization than oral administration of the same drug.

Host factors that impact on the occurrence of adverse reactions include age and sex. Drug allergy appears to be less common and less severe in infants and in the elderly, probably a result of immaturity or involution of the immune system, respectively.²⁰ Women have a 35% higher incidence of adverse cutaneous reactions to drugs than men and a 20-fold greater risk of adversely responding to radiocontrast media.^{6, 27} Genetic factors also play a role in determining some immunologic reactions. Offspring of parents allergic to antibiotics are more likely to develop sensitivity to antibiotics than are children without a family history.² Individuals who have a history of drug sensitivity are more likely to develop additional drug sensitivity. The latter condition has been referred to as *multiple drug allergy syndrome*.⁴⁴ Finally, some disorders may predispose to allergic reactions (i.e., viremia and certain types of antibiotic-related rashes).

LEGAL IMPLICATIONS OF ADVERSE DRUG REACTIONS

Drug injuries of all types frequently precipitate medical negligence litigation. In a large study of closed claims, drug injuries accounted for the highest total expenditure of any type of procedure-related injury.³⁴ The legal system has made it clear that the FDA listing of adverse reactions is held as the standard. The physician must be acquainted with all potential side effects of any drugs being prescribed.¹⁹ The physician must be familiar with the general information in the package insert, which is identical to that found in the Physicians Desk Reference (PDR). Patients have access to the same information because the law requires that they be given the package insert with their drug purchase. The PDR is available in most bookstores as are similar publications such as *The Consumer Reports/Complete Drug Reference Guide (USP)*.

The physician cannot reasonably claim a lack of knowledge about a drug as a vindication. Ignorance of common side effects will frequently be interpreted by the court as medical negligence. Prescribing a drug without a diagnosis makes the physician even more culpable in any future legal action. Deviation from the general prescribing recommendations in the package insert may later be construed by the court as medical negligence. Because the recommendations in the insert are prepared only after extensive trials and later approval by the FDA, they serve as legal notice that any deviation from these directives likely will be translated as negligence. An exception to the latter would be in the instance of a formal clinical investigation in which all the prerequisites, including a formal protocol and full patient consent, have been obtained. In general, there is little recourse if death or disability results from the administration of a drug and the reaction is included in the package insert.

Physician liability for a patient's adverse reaction to a prescribed medication is determined by general standards of due care.⁴⁵ The physician is expected to be the "learned intermediary" between the manufacturer of a drug and the patient for whom it was prescribed. If the patient is harmed by the drug, then the provider will have to testify as to how "learned" he or she really was in that instance. Not only will the prescriber's knowledge be questioned but also the manner in which the drug was prescribed and monitored. If the prescriber used the degree of skill, knowledge, and care that is prevalent in the jurisdiction in which the drug was prescribed and recognized the adverse reaction and effectively managed its symptoms, he or she will not usually be culpable. A patient cannot necessarily infer negligence simply because the results of a course of treatment were unsatisfactory. The provider should be aware, however, of all potential side effects and inform the patient of these potential risks with the

opportunity to refuse the medication. Drug-related liability risks will be minimized if the provider carefully explains all risks to patient and supplements this explanation with plain English warnings related to potential side effects (e.g., copies of the information in The Consumer Reports Complete/Drug Reference Guide or the American Medical Association's Patient Medication Information Program). Be certain to inquire if the patient is allergic to the drug you plan to prescribe. An open question like "Do you have any allergies?" may be interpreted to mean a request about "hayfever."

Continuing to prescribe a drug in a patient having an adverse reaction is evidence of physician culpability.⁴⁰ If, according to the standard of due care, the medication prescribed was not appropriate for the diagnosed ailment, negligence can be assumed even though the adverse reaction that occurred could not have been prevented. On the other hand, if a practitioner knows a specific drug is absolutely indicated for the medical condition but is aware of the possibility of an adverse reaction, yet believes it is reasonable to assume the risk, he or she must first inform the patient and receive consent before proceeding to be legally protected.⁴⁰

THE IMPORTANCE OF INFORMED CONSENT

In terms of medical negligence litigation, the issue of informed consent and its proper documentation looms as one of the most important issues of risk avoidance. Informed consent is a legal doctrine that requires a physician to obtain consent for treatment rendered, an operation performed, or any diagnostic procedures.¹ Informed consent is a process, not a form, and it requires the practitioner (not a delegated representative) to directly discuss therapeutic issues with the patient. The law of informed consent varies significantly from state to state, and physicians should acquaint themselves with the law in their state. In most states, however, the law makes it a nondelegable duty of the treating physician. The doctrine requires that the physician discuss the following information with the patient:

- The risks and benefits of a proposed treatment
- Alternatives to a proposed treatment
- The risks and benefits of alternative treatments
- The risks and benefits of inaction

With respect to drug therapy, the provider has the responsibility of explaining the proper use and potential adverse effects of the prescribed drug and the potential adverse effects of not using the prescribed drug or not using the drug as prescribed. Most importantly, the discussions and decisions regarding prescribed drugs should be documented in the medical record.¹

It may seem unreasonable and unduly burdensome to the practitioner to address these important issues with each medication prescribed. Nevertheless, this is what is expected. The prescriber is legally bound to make a reasonable effort to determine if an adverse drug reaction is likely to occur. The use of a thorough history can mitigate problems related to drug reactions. For example, a careful inquiry as to whether a patient has a history of allergy to the drug that is being prescribed may seem fundamental, but it does surface as a problem. In addition, knowing a patient's habits with respect to alcohol should modify how you prescribe acetaminophen. Also, active smoking may increase the risk of thrombosis with oral contraceptives or alter the metabolism of theophylline in

the body. The practitioner is liable if there is no effort to warn the patient of side effects that can occur while taking the medication. The provider is especially obligated to clearly discuss any possibility of permanent adverse effects by a medication (e.g., sterilization, skin pigmentation). Unfortunately, this communication is frequently not done when medications are prescribed by phone, and when it is, it often goes undocumented. In obtaining consent, the practitioner should discard paternalistic and authoritarian roles and act as a teacher, advocate, and counselor. The patient should be given ample time to weigh the risks, and if there are important ramifications, to discuss them with family (and even another provider) whenever possible. For example, in my own practice, I recently made a diagnosis of hereditary angioedema in a 16-year-old girl whose condition was causing increasing episodic symptoms, including a recent bout of laryngeal edema. In discussing the initiation of androgen therapy, I provided verbal and written information about side effects, had the patient discuss it with family for several days, as well as visit with her mother's gynecologist before commencing the androgen therapy.

RISK AVOIDANCE AND PREVENTION OF ADVERSE DRUG REACTIONS

Physicians occasionally find themselves involved in professional liability claims that are not directed to actual medical negligence but to deficiencies in administrative systems or communications in the practice setting. The allergist or immunologist conducts most of his or her practice in an office setting. Lack of attention to good record keeping or inadequate communication between the physician or his or her staff and the patient can place the practitioner in an indefensible position with respect to the law. Conversely, even in situations in which a deviation in the standard of care has occurred, good patient–relation skills and well-functioning risk management systems can serve to minimize or correct any harm to the patient.

Risk avoidance in the area of adverse drug reactions has a great deal to do with documentation in patient medical records. It is important to remember the adage of the plaintiff attorney, "If it's not in the chart, it didn't happen." Perhaps one of the biggest myths in the area of charting maintains that charting prescription refills is a waste of time. Nothing could be farther from the truth. Charting refills tells the prescriber whether the patient is being compliant with medication instructions. This area of the patient record should be consulted each time the patient is seen. Another myth maintains that there is no need to document out-of-office phone calls, but this would be a grave mistake in terms of risk avoidance. Charting all communications in or out of office is absolutely necessary, especially with respect to decisions about drug therapy. The basic principles of good medical record keeping dictate that the physician review the record periodically to ensure accuracy, legibility, and timeliness of all entries.

Errors in the prescribing of drugs are very common and are a major cause of adverse drug events.⁹ Many specific factors have been associated with prescribing errors, including miscalculations of drug dose, errors in decimal points, medications with similar names, medication dosage forms (controlled release versus noncontrolled release), use of abbreviations, and so forth.³⁰ It is important to keep all of these potential pitfalls in mind when writing prescriptions. The physician should be mindful about the possibility of generic substitution especially with respect to the role of allied health professionals approving the switch.

The simplest way to reduce or prevent drug allergy is to prescribe medica-

tion only when it is absolutely necessary.¹⁶ In a group of 30 people who died of penicillin anaphylaxis, only 12 people had a clear indication for penicillin therapy.⁴¹ Before prescribing any drug, the physician should carefully consider the indications for its use. Before providing any patient with a drug prescription, be absolutely certain there is no history of a prior adverse reaction to that drug or any closely related drug group. In this respect, consider whether the patient has any increased risk of drug allergy (i.e., age, sex, genetic factors, and so forth). If there is any doubt about the increased likelihood of an adverse reaction, consider whether there are any diagnostic studies that could be pursued to detect an underlying sensitivity.¹⁶ When considering administration of a specific drug, if there is a choice, oral administration is always the safest route. The oral route is less likely to sensitize, and the incidence of adverse reactions is less frequent. Further, when adverse reactions occur with oral administration, the reactions are generally less severe.¹⁶ Topical application of drugs should be avoided whenever possible because this route of exposure is much more likely to sensitize. This result seems especially true with penicillin and related β -lactam antibiotics.

SPECIAL RISKS RELATED TO THERAPEUTIC AGENTS IN ALLERGY PRACTICE

Because the specialty of allergy and immunology is centered on the very nature of the allergic response, there is no defense for the allergist who might argue a lack of knowledge regarding an adverse drug effect, especially an allergic reaction. The core of expertise on the nature and incidence of allergic responses should also provide insight into how to identify nonallergic reactions. The allergy specialist should be very well versed in any protocols or guidelines that address how therapeutic agents should be administered in relevant disease states such as asthma,¹⁸ or asthma in pregnancy.³⁹ One can be certain that these nationally distributed critical pathways, guidelines, and protocols will be held up as the standard of appropriate care. Protocols that are widely distributed and outline the preferred approach to the patient with a history of a prior adverse reaction requiring repeat treatment for the same indication should be similarly regarded.¹⁵

Another important area in which the allergist or immunologist has potential exposure is in the administration of allergen immunotherapy. Because allergen immunotherapy is not without risk, communication of that risk with informed consent and attention to the smallest detail is imperative. Written office policies should be in place to guide ancillary staff in what measures to take in the event of any untoward reaction, missed injections, and so forth. This policy should follow as closely as possible the available published guidelines.³⁵

Perhaps the most common disorder the allergist or immunologist evaluates and treats is allergic rhinitis. The management of rhinitis frequently encompasses the use of oral antihistamines. As a class, there are issues related to pediatric labeling, pregnancy, and use in the elderly of which the allergist must be aware. Patient education and informed consent are critical issues in these areas. In the current climate of managed care, the higher cost of the nonsedating antihistamines has resulted in their limited availability on formularies. The practitioner must remember that reliance on sedating antihistamines opens the door to a number of undesirable side effects, including neuropsychiatric problems, lassitude, sedation, and performance impairment.^{26,33} Although sedation is especially troubling, impaired job performance may be equally so and may go unrecog-

nized by the patient. This result has particularly important safety implications in jobs entailing construction, public transportation, manufacturing, and so forth. On-the-job injuries or other untoward events occurring while treated with sedating antihistamines have significant legal implications if the prescriber has not appropriately informed the patient of the risks.

Whenever a patient's condition or medication affects the level of consciousness, the patient may be a threat to themselves and to others, whether driving a motor vehicle, working with dangerous equipment, or being at unprotected heights. In these circumstances, it is the physician's duty to warn the patient not to engage in such activities for the period that the patient is at risk. Such instructions should be documented in the chart. If a practitioner fails to instruct a patient about the risks associated with impairment resulting from medication, and a motor vehicle accident occurs because of the patient's compromised function, the physician may be found liable for some or all of the resulting damages.

CONCLUSION

Individuals in the United States take a considerable number of approved and unapproved drugs. Optimally, the goal of these drugs is to achieve improvement or relief of symptoms. Because there is no such thing as a drug without side effects, however, drug-related problems are quite frequent in the population. Drug-related morbidity and mortality have been estimated to cost more than \$136 billion annually in the United States. This estimate is higher than the total cost of cardiovascular care or diabetes care in the United States—despite the fact that adverse drug reactions are probably under-reported. Many adverse drug problems are the result of faulty system design that either induces errors or makes them difficult to detect. Correction should be focused on a systems approach to absorb errors that do occur and correct them before damage occurs. A classification of predictable and unpredictable adverse drug reactions has been reviewed. The characteristics and risks for immunologic reactions has been discussed in detail. The legal implications of adverse drug reactions in medical negligence litigation accounts for a significant total expenditure of funds. The physician must be familiar with the information in the package insert and is responsible for appropriately informing the patient of all risks and benefits. The issue of liability in these matters always is determined by the general standards of due care. The legal doctrine of informed consent has been defined for the reader in relation to adverse drug reactions. Finally, general measures for risk avoidance and prevention of adverse drug reactions have been reviewed in considerable detail.

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