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*E. M. Goldstein,*[1] *B.Sc., Ph.G.*

# The Medico-Legal Aspects of Drug Interactions

There will always be error produced by failure of human perception. And, undeniably, there will always be occasions on which a drug may be mislabeled, an improper dose administered, or the wrong drug given to a patient. Injury from such situations generally constitutes negligence as a matter of law.

However, the more avoidable injuries are those of adverse drug reactions and drug interactions. Reporting of adverse drug reactions is notoriously poor and only a small percentage of reactions is actually documented. Thus, available statistics have even greater significance. According to early reports, "18 to 30 percent of all hospitalized patients have a drug reaction [*1,2*], and the duration of their hospitalization is about doubled as a consequence [*1–4*]. In addition, 5 percent of all admissions to hospitals are primarily for drug reaction [*1,5*], and 30 percent of these patients have a second reaction during their hospital stay. The economic consequences are staggering: one seventh of all hospital days is devoted to the care of drug toxicity, at an estimated yearly cost of $3,000,000,000. [*6*]" [*7*].

Nearly 80 percent of all drug reactions are reported in the literature as being predictable and preventable. These reactions, clearly due to improper prescribing, cause 1.5 million hospitalizations and 30,000 deaths a year [*8*]. These are the circumstances that surround one of the most frequent causes of medical malpractice claims—drugs.

## Adverse Drug Reactions

A significant percentage of adverse reactions results from failure to heed the warnings accompanying a drug. During recent federal hearings of the Senate Monopoly Subcommittee, chaired by Senator Gaylord Nelson, physician misuse of many therapeutic agents was stressed. At these hearings, the director of the Bureau of Drugs of the Food and Drug Administration (FDA), Dr. Henry E. Simmons, testified that doctors are treating millions of people with unneeded antibiotics, causing tens of thousands of deaths yearly. Dr. Simmons and other experts pointed out that 60 percent of hospital patients who receive antibiotics don't need them. Similarly, 60 percent of people who complain of cold symptoms are given prescriptions for antibiotics by their physicians. Dr. Simmons also said that the sharp rise in hospital superinfections was a "major problem" and added that "there may be 100,000 to 300,000 cases (of adverse drug reaction) each year, of which 30 to 50 percent are fatal [*9*]."

The therapeutic agent that has become a classic example of the unheeded drug warning is the antibiotic chloramphenicol. After its introduction in 1949, many reports began to

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[1] Executive director, American Association of Medico-Legal Consultants, 2200 Benjamin Franklin Parkway, Phila., Pa. 19130.

emerge regarding its role in the causation of severe bone marrow depression, terminating in aplastic anemia, a fatal blood disease. Despite these reports, physicians had prescribed it for an estimated 40 million people by 1960. During the next twelve years there were rounds of federal hearings and periodic warnings were issued by the manufacturer, the FDA, and the American Medical Association (AMA) Council on Drugs on the risks associated with the use of chloramphenicol. In addition, the warning, appropriately rimmed in black, was prominently displayed on every product insert, advertisement, and in *Physician's Desk Reference* (*PDR*). Moreover, there were many highly publicized product liability and medical malpractice actions for cases of aplastic anemia induced by administration of chloramphenicol for trivial infections that could have been effectively treated with less toxic agents. For many years, it has been generally accepted that chloramphenicol should be prescribed only for a few rare and serious conditions. Yet FDA data indicate that more than 600,000 patients received chloramphenicol in 1972. In the face of these adequate warnings, why is this drug still administered? The obvious conclusion must be that drug warnings mostly go unread. In a study designed to predict the prescribing behavior of physicians in private practice by examining attitudes on prescribing chloramphenicol, those who considered themselves well trained in therapeutics generally prescribed the drug less [*10*].

Chloramphenicol is not the only antibiotic misused despite adequate warning. The relationship between the administration of tetracycline to children and subsequent permanent discoloration of the teeth was suggested over sixteen years ago. Since the tetracyclines easily cross the placental barrier, administration to pregnant women after the first trimester may also cause adverse effects on the fetus as deposit of tetracycline in teeth is permanent. In general, between the fourth month of gestation and age seven or eight, tetracycline may cause discoloration of teeth and affect calcification of enamel and dentine in deciduous and permanent teeth. Despite warnings in product inserts and the *PDR*, and a number of successful lawsuits, tetracyclines still remain very popular for pediatric conditions that could readily respond to other antibiotics. Either doctors are unaware that the drug they prescribe is a tetracycline, since there are many trade names, or they are still unaware of the risks of tetracycline administration to children.

### Medico-Legal Actions

Many malpractice cases have been filed because of wrongly prescribed antibiotics. One such case involved a 58-year-old salesman hospitalized for minor foot surgery. Curiously, his surgeon placed him on preoperative prophylactic kanamycin because of cardiac disease history. The drug was continued for a week after surgery, during which time no blood urea nitrogen (BUN) determinations were made. As a result, the patient lost his hearing as well as his bunion. Assuming that there was a rationale for prophylactic therapy, a less toxic antibiotic could easily have been chosen.

Other malpractice actions are provided by the experimental use of drugs. Methotrexate, a cancer chemotherapeutic agent, has recently received FDA approval for use in treatment of psoriasis. For 10 years prior to approval, its use in dermatology was highly experimental. A $600,000 medical malpractice suit against a dermatologist in Maryland was won after the plaintiff developed aplastic anemia, for example [*11*].

There are a number of lawsuits now pending throughout the country on hepatocellular necrosis or fatal bone marrow depression, both occurring following the use of methotrexate in treatment of psoriasis. There is also evidence that this anti-cancer agent may be carcinogenic [*12–14*]. Since the immunologic functions of the lymphoid system are thought to provide a defense against neoplasia, an immuno-suppressive agent such as this

folic acid antagonist could, in theory, favor tumor emergence, growth, and metastases. While this risk may be warranted in cases of known cancer, the use of this drug in treatment of psoriasis, regardless of its alleged efficacy, is replete with medicolegal complications.

Paradoxically, malpractice liability may also exist for a failure to prescribe a needed drug. There have been a number of suits alleging the failure to utilize the proper antibiotic. Similar cases have involved various antitoxins and toxoids such as tetanus and snakebite.

**Adverse Drug Interactions**

In the past, adverse reactions to single agents have accounted for the majority of drug-related malpractice actions. However, many recent suits have involved multiple drug therapy. Since time immemorial man has dosed himself with a variety of drug combinations. Far from being a modern innovation, polypharmacy has roots in ancient Greek, Italian, and Chinese medicine. Thousands of years ago the Chinese were certain that combinations of medicine would "stir up a commotion in the patient, or the disease will not be cured by it." In the 12th century, Nicolas of Salerno, director of the medical school, encouraged polypharmacy. He used 35 to 48 ingredients in his "confectio" remedies [*15*]. The difference in today's polypharmacy is that modern drugs are significantly more potent and effective in influencing physiological systems. Physicians are today "creatively" prescribing drugs in combinations never before tried in man or animal. While data on the adverse effects of a single drug are well documented [*16,17*], the toxic potential of multiple drug therapy has received little attention until recently. It has been estimated that drug interactions form 19 to 22 percent of causes of all adverse reactions [*18*].

Though some interactions are well documented, many have only been theorized on the basis of anecdotal data. With very few exceptions, the overall clinical consequences of drug interactions are unknown [*19*]. To further complicate the situation, most of the present knowledge of toxicities of drug combinations has been obtained from experiments on animals; and there is, unfortunately, no certain method for ascertaining the relevance of animal data to man [*20*]. Drug interactions are probably quite common, considering the number of drugs prescribed in combination, and it is really surprising that so few have been documented. One reason reporting may be inadequate is the therapist's reluctance to attribute adverse change in a patient's condition to a drug that was supposed to effect an improvement [*21*].

Chance recognition of unexpected drug interactions is slow and inefficient [*22*]. The problem is compounded when the interaction has not been previously described. Practicing physicians tend to doubt their observations of drug interactions unless that interaction has been previously reported. In some cases the clinical situation is too complex to allow recognition that an unexpected event in a patient's course of treatment is related to drug therapy. Even when an abnormal response is clearly recognized, it is usually attributed to factors other than drug interaction. Physicians frequently fail to report drug interactions, even when recognized as such, since the physician is concerned about his liability in such cases [*23*].

There is little doubt that multiple drug therapy is more frequent than single agent administration. But how prevalent are such combinations? A survey in a Baltimore hospital revealed that patients who were receiving a new type of penicillin also received no less than six other medications during the time of the survey [*24*]. Another multiple drug therapy study showed that some patients receive an average of 14 different drugs while hospitalized; another survey found that 10 was the average [*25*]. The literature shows that hospitalized patients generally receive from 8 to 25 drugs during a single admission, a large number being given simultaneously. Under such circumstances, the patient has at

least a 40 percent chance of having an adverse reaction to one or more of the drugs [7]. One must remenber that adverse drug interactions occur not only because a drug may extend the pharmacological action of another, but also because a drug may prevent the therapeutic effect of another and thereby lead to progression of the disease being treated. The latter adverse effect is difficult to detect and often overlooked [*26*]. Sometimes more harm is done to a patient on multiple-drug therapy than would ever have occurred from the ailment being treated [7]. Therapeutic misadventures such as this may result in malpractice suits.

### Multi-Drug Interactions

In recent years there have been numerous attempts to correlate the data available on drug interactions. A number of review articles [*27–43*] and texts [*44–54*] have appeared describing the interactions of two agents, and a few of these discussed the results of these interactions. However, there is virtually no existing documentation on multiple-drug interactions so that the pharmacological effects are essentially unknown. If we assume that the mean number of drugs ingested by a hospitalized patient is 10, then the risk of developing an adverse reaction, including death, increases almost geometrically [*25*]. When many drugs are used together, one must be concerned with the results of every possible combination. This means that not only may all given drugs interact, but all possible combinations may interact. In a previous paper [*55*] I projected this mathematical progression: if six drugs are administered simultaneously, $2^6$, or 64, interactions are possible. In such cases, the physician exposes the patient to 64 possibilities of danger, not just six, and the danger increases with the number of agents used.

In an extensive and sophisticated statistical exercise involving the principles of "permutations and combinations," Calesnick et al [*56*] developed a most interesting and probably more accurate conclusion (see Table 1). On the assumption that the average hospitalized patient receives 8 different drugs during a 24 h period, there is a theoretical possibility of over 109,000 different drug-induced toxicities or interactions. This would require, on a mathematical rather than pharmacological basis, a maximum of 394,352 individuals to demonstrate each different type of drug interaction (see Table 2). While far from the realities observed in clinical practice, these figures do illustrate the theoretical potential for harm in multiple drug therapy.

These mathematical progressions are almost infinite when applied not only to interactions of legend drugs but also to legend drug interaction with over-the-counter drugs, parenteral fluids, diagnostic tests, alcohol, insecticides, and various clinical conditions.

TABLE 1—*Total number of possible drug interactions and drug toxicities. Courtesy of B. Calesnick et al* [56].

| Number of Drugs | Number of Drug Interactions | Number of Drug Induced Toxicities |
|---|---|---|
| 2 | 2 | 4 |
| 3 | 12 | 15 |
| 4 | 60 | 64 |
| 5 | 320 | 325 |
| 6 | 1 950 | 1 956 |
| 7 | 13 692 | 13 699 |
| 8 | 109 592 | 109 600 |
| 9 | 986 400 | 986 409 |
| 10 | 9 864 090 | 9 864 100 |

TABLE 2—*The number of possible patient complexes due to different interactions. Courtest of B. Calesnick et al* [56].

| Number of Drugs | Number of Patient Complexes |
|---|---|
| 1 | 0 |
| 2 | 2 |
| 3 | 12 |
| 4 | 72 |
| 5 | 500 |
| 6 | 4 050 |
| 7 | 37 632 |
| 8 | 394 352 |
| 9 | 4 596 552 |
| 10 | 60 755 472 |

Then, if one multiplies drug combinations by the hundreds of toxicants found naturally in foods, the probability of side-effects and untoward reactions overshadows the therapeutic potential of the drug combinations [*55*].

### Medico-Legal Actions

Clinically significant undesirable results of drug interactions are becoming more and more the basis for malpractice claims. Oral anticoagulants, for example, interact with certain drugs to cause serious hemorrhage. In one malpractice suit the following drug history was found: the patient had been maintained on the anticoagulant warfarin and the anticholesterolemic agent clofibrate; for an "upper respiratory infection" he was given tetracycline and aspirin; he was also told to use chloral hydrate and a laxative as needed. Because all these drugs interact to increase the prothrombin time-response to oral anticoagulants, the patient died of hemorrage [*57*].

In another example, a man in traction received multiple sedatives, including propoxyphen, meperidine, a phenothiazine, and barbiturates. While drowsy and lethargic he fell and injured his leg, producing a thrombophlebitis. He subsequently developed a pulmonary embolism which was agressively treated by the combined use of heparin and warfarin. Within a few days he died of massive hemorrhage [*58*].

### Recommendations

Since adverse reactions from multiple drug therapy are largely unpredictable, conservative prescription practices using fewer agents (no more than two when possible) may aid in avoiding medical malpractice claims. Here are some other rules for the physician who wishes to protect himself against liability and his patients against drug toxicity [*59*].

(1) *Don't prescribe contraindicated combinations.* Medicolegal complications may arise from failure to heed a manufacturer's warning. Should injury occur as a result of using such a drug, it may be considered malpractice. Don't hold the mistaken impression that a small dose used for only a few days is an exception to the rule. Damage has occurred with very small quantities. Chloromycetin can cause aplastic anemia with a single 500 mg capsule. Tetracycline has been shown to cause permanent grayness of children's teeth after one treatment.

(2) *Develop an order of priority of need.* Use as few drugs as possible and exclude those not absolutely necessary. For example, drugs acting on the central nervous system (sedatives, tranquilizers, stimulants) create difficult-to-detect interactions.

(3) *Don't prescribe a new or little-used agent in combination with other drugs.* Use it alone until its action is evident.

(4) *Prescribe drugs for a limited time only.* Long-term therapy may result in different effects than those gained in short-term usage.

(5) *Be sure of kidney and liver function.* Illness changes physiological systems and thereby alters drug action.

(6) *Don't be misled if a multiple drug combination is tolerated by one patient.* Other patients may be slow inactivators who will produce higher plasma levels at the same dosage.

(7) *Reduced effectiveness and toxicity are both common in drug interactions and may occur simultaneously.* An example is a drug failing to maintain blood pressure because of concomitant interfering agents.

(8) *Multi-drug therapy may limit the beneficial effect of a single agent and lead to the progression of a disease.* For example, if tetracycline and penicillin are given together, the tetracycline may prevent the suppression of penicillin-sensitive organisms by inactivating the mechanism by which penicillin works.

(9) *Know which patients are seeing other physicians and what medications have been prescribed.* This is easier said than done. At minimum, all medications should be labeled so patient (and other physicians) know what is being taken.

(10) *Know what over-the-counter drugs patient is taking.* This requires specific questioning. Check for interaction with prescription drugs.

While the courts recognize the inherent risk in the use of any drug, physicians are being held liable more and more often for adverse effects of the drugs they prescribe. If the use of a drug is a variation from accepted practice of the medical profession, that use would be "experimental" in a legal sense and place liability upon the prescribing physician [*60*].

The guidelines a physician uses in prescribing drugs are determined by a number of factors, including information supplied by the manufacturer, FDA regulations, and standards of his profession. The drug manufacturer's legal responsibility is compliance with FDA requirements, which includes warning of adverse effects of a drug. FDA regulations do not, however, establish standards for physicians. The information in the approved package insert can only bring a drug's possible hazards to a physician's notice. In the event of litigation, deviation from the warning's limitations will require him to substantiate his reasons for doing so. If the court decides the package warning is adequate, responsibility shifts from the manufacturer to the physician, who must then show he has obeyed the definition of the "general standard of care." The standard of care in a professional action is usually judged by what one's fellow physicians would do in similar circumstances. These standards are created of many factors, including the literature, the drug manufacturer's recommendations, the opinions of experts, and the regulations and customs of the local and national community. A physician may use a drug in any manner he regards as the "best interest" of the patient, but his medical judgment will be measured by the standard of care if the patient is injured by that drug [*61*]. One does not generally prescribe a potentially toxic antibiotic for a trivial medical condition; a busy physician who fails to read the fine print of a drug warning may find, to his dismay, that a known toxicity does exist—when the warning is enlarged to poster size and used in the courtroom at his trial for malpractice [*62*].

**Summary**

Recently there have been a number of drug combinations recalled by the FDA because of failure to show efficacy. However, there are neither standards nor regulations preventing

physicians from prescribing multiple drug combinations in which they have no clinical experience. Therefore, each new combination is in reality an experiment and each patient a test case.

It is an interesting question whether there should or could be developed a medical standard of care in the prescription of multiple drugs. Does the normally prudent physician commonly prescribe 10 drugs simultaneously? Probably not. Is the prescription of three or four drugs "bad" medicine? Perhaps this is a question for forensic science and case law to answer. It seems to me, as a consultant in forensic aspects of pharmacology, that ultimately there must develop a standard of care in the use of medicines, requiring of the practicing physician a certain basic knowledge of drug interactions.

Where does the basis for sound therapeutic understanding begin? Such knowledge is supposedly attained during a physician's medical training. The study of drugs, it is assumed, is a significant percentage of the physician's education. However, the curriculum of most medical schools includes a mere six months of freshman pharmacology. Moreover, there are presently over 130,000 drug entities, drug combinations, and dosage forms listed in the *PDR*, and the number increases yearly [*63*]. These do not even represent the complete armamentarium of prescription drugs available to the practicing physician. To complicate the picture, approximately 75 percent of the agents available were not even on the market 15 years ago, when more than half the nation's physicians were in medical school. Finally, the physician's continuing education since taking that freshman pharmacy course has largely been conducted by various "detail men" (salesmen for pharmaceutical firms), most of whom are neither physicians nor pharmacists. Obviously, the priorities of the drug industry differ from those of academia, but the basic problem for both is a lack of accurate transmittal of vital information.

The physician has become the victim of an archaic educational system that provides meager exposure to the drug field but expects him to prescribe knowledgeably. Drug information, especially warnings about interactions, has become too voluminous and complex for the lone practitioner to stay abreast of. The sole bases for therapeutic understanding, drug mechanisms, were taught long ago in that freshman course and have been forgotten by most. It is the system that must change to provide the information necessary to avoid liability as well as the potential for destruction.

The solution may rest in the future of the clinical pharmacologist, a specialty just beginning to emerge and not as yet strictly defined. The recruitment of physicians and pharmacists into the discipline of clinical pharmacology should be a major goal of the nation's medical schools [*64*].

The issues of the future are of greater consequence than the malpractice suits to come on drug reaction and interaction. The current drug situation will mushroom into catastrophic proportions over the next two decades if physicians now being trained are not more adequately trained in pharmacological knowledge.

As Oliver Wendell Holmes, Sr., the physician, commented about 75 years ago, "If the entire pharmacopeia were cast into the sea, it would be so much the worse for the fishes and so much the better for mankind." Those of us who are aware of the potential problems sometimes feel that way today.

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American Association of Medico-Legal Consultants
Park Towne Place North
2200 Benjamin Franklin Pkwy.
Philadelphia, Pa. 19130