The Medicolegal Significance of the Package Insert

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The medicolegal significance of the package insert is expanding. The use of the package insert is increasing in determining negligence in medical malpractice suits against physicians and hospitals. There is a determined movement in the United States to extend the inclusion of the package insert to all patient prescriptions beyond the present requirement that it be included with contraceptive pill packets.

Although the Food and Drug Administration (FDA) recognizes that the package insert supplies authoritative, substantiated information upon which the physician and patient can rely, there are a number of unanswered questions which particularly create dilemmas for the physician.

Not only does the role and power of the FDA with regard to the package insert remain unsettled, but the FDA has issued vague, ambiguous, and inconsistent policy statements regarding the legal significance of the package insert. This is particularly critical in setting the standard of care for prescribing by physicians. Furthermore, the package insert has serious medicolegal shortcomings. It frequently does not contain all available information, and lags behind known accepted data. In addition, the courts are not uniform in recognizing and accepting the FDA's policy statements.

The purpose of the paper is to amplify, analyze, and explain these problems. Courses of action for prescribing, based on established legal duties and responsibilities, are suggested for physicians. Some appropriate principles of law are reviewed with the purpose of minimizing legal expense and liability.

A study by the Commission on Medical Malpractice of the US Department of Health, Education, and Welfare indicates that drug-related malpractice accounts for ten percent of all cases.[1] These lawsuits include the use of the wrong drug, improper dosage, failure to promptly diagnose and treat adverse reactions, and failure to warn patients of reasonably forseeable side effects.[2,3,4] One recent development that could portend serious legal problems for physicians is the increasing pressure for generic substitution.[5]

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As a result of the enormous growth in the number of new drugs in the last decade, it has become difficult for most physicians to keep informed about drugs through the usual medical media. The package insert grew out of a need to present physicians with accurate information regarding a drug, apart from that imparted in the advertising and promotional literature of the pharmaceutical manufacturer. Articles and advertising in medical journals as well as drug manufacturers' promotional activities including literature and visits by representatives were the main sources of new drug information. Unfortunately, physicians were not always made aware by the drug manufacturers of a drug's side effects, contraindications, and incompatabilities, nor were all journals readily accessible to physicians. Yet the courts have required physicians to be aware of and implement new information on drugs.[6,7]

In an attempt to remedy the situation, the FDA in 1961 promulgated a regulation that provides for a package insert to be on or within all bulk prescription drug packages. It is known as the "full disclosure" regulation and requires that labeling on or within the package from which the drug is to be dispensed bear adequate information for its use. This includes indications, effects, dosages, routes, methods, and frequency and duration of administration, as well as any relevant hazards, contraindications, side effects, and precautions under which practitioners licensed by law to administer the drug can use it safely and for the purposes for which it is intended. This includes all purposes for which it is advertised or represented. The package insert was not intended to convey other information, for example, that relating to the diagnosis and treatment of disease. In essence the package insert denotes the drug's dosage, safety, and efficacy.[8,9]

In order for an indication to be listed on the package insert, it must have been proved that the drug is safe and effective for the designated purpose. The FDA considers the insert to have a twofold purpose: to alert physicians to the conditions under which the drug is acceptable and prescribable; and to limit the claims manufacturers can make about drug products.

Legal Status — Friend or Foe?

In these malpractice-conscious times, how important is this little document, the pharmaceutical package insert, to the physician? There is significant agitation to include the package insert with all filled prescriptions. This is now required with the dispensing of the contraceptive pill package. Just what effect would a patient prescription insert have on malpractice? Before that question is addressed, some background on the package insert would be helpful.

At present it is still uncertain whether the pharmaceutical package insert is a legal document or just an informative piece of literature. The requirement that the document accompany all packages of drugs has created a controversy and division of authority regarding its legal status. Does the package insert set the stan-

dards the physician must follow, and has it increased his/her liability for the administration of new drugs or of old drugs for new uses? What if the physician strays from the approved usage and dosage schedule as set forth by the package insert? To put it another way, is the insert merely a label to be used in an advisory manner by the physician, or is it a "legal" document admissible in a court of law as sole proof that the physician has negligently departed from the usages and dosages stated in the insert?

The FDA has made several assertions, some seemingly contradictory, on this matter. Three in particular shall be examined.

1. The FDA has indicated that it regards the package insert as a part of the labeling of the drug. Although it is established legally that drug labeling is not binding, a few courts have decreed that the package insert itself defines the standard of care, and any deviation from it is prima facie evidence of negligence. Physicians' response has been to call it a therapeutic straitjacket. Some claim that the insert passes the whole responsibility for medication to the physician, and that if physicians adhered to the letter of every insert they would not prescribe any drugs at all.

Some physicians want to see the package insert dramatically changed, its quasi-legal status eliminated, giving way instead to a solely educational function. For the time being, it is unlikely that such changes will be made. It seems more likely that the FDA may move in the opposite direction.[8]

2. The FDA has indicated that the package insert is not intended under the law to serve as a totally current repository of all the information regarding the drug. In fact, it is well known that the package insert is frequently behind the times. The FDA admits that the insert contains only those indications and usages based upon substantial evidence of safety and effectiveness. However, the FDA has also said that it does consider the package insert to be an authoritative document of particular importance, clearly indicative of a standard of care that should be followed by physicians.

3. The FDA has indicated that good medical practice and patient interests require that physicians be free to use drugs according to their best information.[10] Mistakes or errors involving the usage of a drug are not a violation of the law of negligence. However, when a physician prescribes a drug for a use not in the approved labeling, he or she invokes two responsibilities. The first is to be well informed about the drug and to base the use of it on firm scientific rationale and sound medical data. The second is to be ready and able to cite a text, journal, or article, or show that the use is reasonable and consistent with the sound practice of medicine. This should not be insurmountable, as many uses of drugs for unlabeled indications are widely accepted and fully established long before the use is approved by the FDA. The physician cannot ignore the package insert, however.

Although the insert does not restrict physicians to using a drug only for labeled indications, any physician deviating from the package insert might be called upon to defend such a departure in a lawsuit. In a malpractice suit the judge can permit the admission of any labeling as evidence, and instruct the jury to consider the insert as an indication of the standard of care. The pharmaceutical package insert has figured in judgments against members of the health-care industry involving significant awards.[11] For that reason, physicians must be as cautious in using an old drug for a new use as in using a new drug. The medicolegal significance of the patient prescription insert can be inferred from the experience with the pharmaceutical package insert.[12]

Legal Implications

There is widespread uncertainty regarding the legality of using accepted drugs for unapproved uses and using drugs not approved by the FDA. This undoubtedly grows out of an ambiguous understanding of the responsibilities and powers of the FDA and the legal status of the package insert.[13] This, in turn, arises from the seemingly inconsistent policy statements issued by the agency. The FDA has on occasion declared that from its standpoint the package insert is nothing more than controlled advertising. At other times the agency has declared that is considers the package insert authoritative. Asked to interpret that declaration, the FDA has explained that it means that the insert is medically sound. It wants physicians and patients to know that the package insert is supported by substantial evidence and both parties can rely on what they read in the insert.

Unfortunately, there are numerous gaps existing between accepted medical practice and the various package inserts. The FDA generally deals with a particular usage of a drug only when the pharmaceutical company wants to include it in the insert. Therefore, it is important to note that if a use is not included on the insert, there is no implication that scientific evidence does not exist for that use of the drug. It may mean only that the FDA has not been asked to review such data. Usually the omission occurs because the pharmaceutical company does not have enough of a market to make it economically feasible to undertake the studies to justify that use of the drug to the FDA. Physicians then need not be intimidated from using an accepted drug for an unapproved use when it is medically sound.[14]

Since the package insert represents only the submitted prescribing information, it can be argued that it is not intended to nor can it tightly circumscribe the physician's use of a drug. As in all medical situations, the physician's studied professional judgment and discretion dictate variation in usage and dosage from that recommended on the insert. Following this line of argument, use of a drug, once it is marketed, is the practitioner's responsibility, medically and legally.

What may happen legally if the physician prescribes an investigational drug or an old drug for a new use? As long as there are no adverse reactions, nothing is likely to happen legally. On the other hand, if there is an untoward effect, the burden of proof will certainly rest with the physician to demonstrate that that use of the drug was not inconsistent with accepted or good medical practice. The physician can show this by means of scientific medical treatises and articles, clinical reports on the use of the drug, or by the practice of other reputable physicians. This is not an unreasonable burden.

Furthermore, withholding a drug may be the wrong course of action. Malpractice can be charged if it can be shown that an investigational drug or an approved drug (but for an unlabeled use) was withheld when it

could and should have been administered. Good medical practice at times requires administration of a drug in the face of known side effects. The matter is one of calculated risk.[15-19] If the patient's condition warranted use of a drug and no other drug were as effective, the physician would not be held liable if side effects occurred.[20]

The decisions, interpretations, and conclusions of the FDA are not legally binding on physicians or courts. Even the FDA's most rigid interpretations of its drug labeling regulations, which include the package insert requirement, denote that it merely contains adequate information under which physicians can use the drug safely for the purposes for which it is intended and listed, including all purposes for which it is represented or advertised. There is no explicit prohibition against the use of the drug in an unapproved manner. Most courts have accepted the FDA's interpretation of its own regulations. However, some courts, despite the FDA's interpretations, consider the package insert information as prima facie evidence of the standard for the drug's use. Regardless, the package insert is merely one piece of evidence. Ultimately, any controversy would be settled in that area by a judge or jury.

Critical to the physician's use of drugs in ways not approved by the FDA is the legal requirement of informed consent. The best defense the physician has is proof of informed patient consent. The fact that the patient has been informed should be recorded on the chart (including date and time). To that end, the patient should clearly understand when he or she is taking a drug for an unapproved use and not for an established use. The patient should be warned of all reasonably forseeable risks and mishaps. Patients should be told about potential drug reactions, particularly self-detectable reactions. The physician is not duty-bound to recite the whole package insert, but if the insert is given to the patient, the physician is legally required to ascertain the patient's comprehension. In order for patients to be able to detect certain adverse reactions, they have to be alerted to them. Failure to warn is a major problem now. Not only is it good medical practice, but fully informing the patient allows a sharing of the burden of the risk-taking decision between physician and patient.

What should a physician do when contemplating the use of an approved drug for an unlabeled or unapproved use? Many physicians now are disinterested in finding new uses for the old approved drugs because they realize that they may be called into court to account for the use of drugs, even for labeled indications. Some physicians believe that unlabeled or unapproved prescribing is illegal or at best extralegal. However, the prescribing of an approved drug for an unspecified or unapproved use is not illegal. On occasion, such prescribing may actually be required in the exercise of good medical judgment.

A critical example of the medicolegal uncertainty revolving around the package insert is what has been termed the "therapeutic orphan" phenomenon. Numerous package inserts do not contain information regarding the use of the particular drug in children and pregnant women. Since these two classes of people are not available for drug evaluation, neither the drug company nor the FDA can list the appropriate data. What is the physician to do when pediatric and obstetrical drug data are not available? These patients frequently require therapy and obviously must be treated with drugs actually not approved by the FDA specifically for them. It is reasonable to assume that unless a drug is specifically proscribed for these groups, the physician may use it in children and pregnant women in appropriate dosages with adequate clinical and laboratory observation and follow-up. A clear understanding of the situation with the patient or parents, and their approval, should essentially eliminate any liability.

If the physician prescribes a drug according to the package insert, does that protect him/her from all liability?[21] Of course, prescription of a drug in ignorance of available information regarding its potential harm is clear negligence! If there are warnings about the drug in sources other than the package insert, particularly in medical journals, the physician is held accountable for those warnings, as well as for knowledge available from any source, including his/her own experience. Strict adherence to the package insert does not afford immunity from liability when the insert is barren but the information is available elsewhere.

From this discussion it is apparent that there exist conflicting interpretations of the legal implications of the FDA-approved package insert. There also remains the question as to the individual physician's obligation as a result of the printed material. While it is critical to remember that the FDA does not have the power to control physicians and dictate the practice of medicine, particularly when it comes to prescribing drugs, the physician should bear in mind that courts do have the power to rule on a use of a drug retrospectively. Ultimately, any controversy would be settled in that area by a judge or jury. Unfortunately, the legal significance of the package insert, like many legal doctrines, varies among the various jurisdictions. It therefore behooves the physician to investigate the legal status of the package insert in his or her jurisdiction. With that knowledge the physician can better support his or her use of a drug whichever legal status the courts ultimately assign the package insert.

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