

Chapter 27

Medication Errors

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Types of Medication Errors
Medication Use Process
System Errors
Which Drugs Are Most Often Involved in
Medication Errors?

How Has Modern Research Improved Therapeutics and
Reduced Drug-Related Morbidity?
Implications of Pharmacogenetics and
Pharmacogenomics on Medical Negligence

Since the publication of the Institute of Medicine's (IOM) report, *To Err Is Human: Building a Safer Health System* in 1999¹, health care professionals, legislators, attorneys, and the public have developed an increased awareness of medical error and the need to reduce avoidable morbidity and mortality. Despite increases in technology and the introduction of new medications into the physician's armamentarium, today's practice of medicine is still plagued by the human factor, which contributes to error.

Another major factor contributing to medication errors is the complexity of the system in which physicians, nurses, and pharmacists practice their professions. In the hospital setting, a physician writing a medication order for a patient has to wait until that order has been transcribed, sent to the pharmacy, and brought back to the floor, before that medication can be administered to the patient. Lucien Leape, MD, one of the authors of the IOM study, has estimated that there are up to 20 steps involved with the prescribing/transcribing/dispensing/administration process in a paper-based (noncomputerized) hospital setting. With so many interim steps to traverse, it is no wonder that errors occur. Contrast that scenario to one in which a physician writes a prescription for a patient in an outpatient setting. The patient takes the prescription to the pharmacy and the pharmacist fills it. Simplicity supports safety. The fewer steps involved in the process, the lower the likelihood for error.

However, error has a different meaning to some health care practitioners. One physician, when told he was going to be sued for a medication error, retorted, "How can they sue me, I didn't intend to give the patient the wrong medication?" Webster's *New Collegiate Dictionary* has several definitions of "error," but the one that seems to be most appropriate in the context of "medication errors" is "an act that through ignorance, deficiency, or accident departs from or fails to achieve what should be done."

According to the National Coordinating Council for Medication Error Reporting and Prevention (NCCMERP), medication error is defined as:

any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is

in the control of the healthcare professional, patient, or consumer. Such events may be related to professional practice, healthcare products, procedures, and systems, including prescribing; order communication; product labeling, packaging, and nomenclature; compounding; dispensing; distribution; administration; education; monitoring; and use.²

The key word in the dictionary's definition of error is "departure" and the key word in the NCCMERP definition is "preventable"; intent is not an issue. The dictionary definition also mentions "ignorance" and "deficiency" as being causes of error, two factors also identified in the contemporary literature on medical and medication errors.

Ignorance can be remedied by providing physicians with the knowledge they need about the medications they are prescribing, along with information about the patient's allergies, concomitant medications, current hepatic and renal function, and secondary diagnoses. Deficiencies in the current systems that supply critical information to the physician must be reengineered to make errors more difficult to commit. Many risk management and patient safety experts recommend the application of Failure Mode Effect Analysis (FMEA) to determine the parts of the information transmission system that failed.

The concept is that if it was an error, then it can be prevented. Implementing safer practices requires developing safer systems. Other major causes of medication errors are poor oral or written communications. Enhanced communication skills and better interactions among members of the health care team and the patient are essential to reduce errors.

Lastly, reducing medication errors is an ongoing process of quality improvement. Sloppy handwritten medication orders should be replaced by computerized physician order entry (CPOE), a very effective technique for reducing prescribing/ordering errors, in hospitals fortunate enough to be able to afford costly software. For hospitals with fewer resources, less expensive yet effective change could involve retraining physicians to write all drug orders in plain English, and prohibiting the use of confusing shorthand abbreviations that are subject to misinterpretation, such as QD and QOD, which are among the unapproved

272 Medication Errors

abbreviations referred to by the Joint Commission for the Accreditation of Healthcare Organizations (JCAHO) in their 2005 National Patient Safety Goals. The ultimate goal is clear, seamless, computerized integrated medication delivery instituted by fully-informed health care professionals who are adequately trained to utilize such technological advances.

TYPES OF MEDICATION ERRORS

Classically, there are still five basic types of medication errors, collectively referred to as “the five wrongs.” These include: wrong drug, wrong dose, wrong route, wrong time, and wrong patient. Failure to monitor and/or follow up is also frequently mentioned as a cause of medication errors. With the exception of failure to monitor, the “five wrongs” usually occur as a result of some vague or ambiguous form of verbal or written communication. When drug names look alike or sound alike (e.g., Enalapril® and elerpryl or Lamisil® and Lamictal®) there is an increased risk of misidentifying one drug for another, especially during an oral or telephone order. Recognizing “look alike” drug names, and storing them in different areas of the pharmacy and drug cabinets on the floors, reduces the risk of dispensing or administering the wrong one. Writing both the brand and generic names on the medication order or prescription, followed by the condition to be treated, e.g., Lamictal® (lamotrigine) for seizures, minimizes the likelihood of reported confusion with the similar sounding antifungal, Lamisil® (terbinafine). The United States Pharmacopeia (USP) has compiled a list of “paired drugs” that are commonly mistaken for one another. The list covers several pages and demonstrates that this problem is a source of great concern for quality improvement specialists, physicians, pharmacists, and nurses.

Failure to monitor is another common cause of adverse reactions to medications, especially narcotics. Patients who receive parenteral narcotics in the hospital frequently develop itching from histamine release, a well-known effect of most narcotics. To treat the itching, an antihistamine like diphenhydramine (Benadryl®) may be prescribed. If the patient has already received promethazine (Phenergan®) or hydroxyzine to potentiate the analgesic effect of the narcotic, then the concomitant administration of another antihistamine may intensify the respiratory depressant effects of the other drugs and produce a respiratory arrest. In the evening, patients often receive a benzodiazepine or other hypnotic for sleep, which also may contribute to respiratory depression. Once the patient has been “tucked in” for the night, the nurse may not return to assess the patient or take vital signs until the patient’s oxygen has already desaturated and the patient is found cyanotic or begins to fibrillate.

Failure to monitor in the outpatient setting has a different appearance. A typical scenario may look like this. A patient is discharged from the hospital with a new set of medications and/or several new prescriptions. The patient is elderly and does not walk or drive. The new prescriptions are never filled and, after the patient runs out of the

medication he or she was given at discharge, the new medications are no longer taken and the patient’s health deteriorates, or the patient has to be readmitted to the hospital in urgent or critical condition. Unfortunately, this is an all too common situation.

In order to avoid medication errors of this type, the JCAHO has listed among its 2005 National Patient Safety Goals, the need to reconcile medication across a continuum of care. This means that a JCAHO-accredited facility must ensure that upon admission and upon discharge, the changes in a patient’s medication regimen are “reconciled” (listed) and that changes in medications and dosages are correctly recorded and implemented. Some hospitals utilize nurses or pharmacists to call patients after discharge to verify that new prescriptions have been filled and that the patient is taking his or her medications according to the most recent orders of the prescribing physician. The Visiting Nurse Association (VNA) can also play a valuable role in helping to ensure that newly prescribed medications are taken as directed.

MEDICATION USE PROCESS

The Medication use process (MUP) encompasses all the individual components of prescribing, transcribing, dispensing, and administering medications, and monitoring their effects on the patient. The process can be schematized as shown in Fig. 27-1.

Table 27-1 shows the results of studies conducted by the Agency for Healthcare Research and Quality (AHRQ) to determine at what stage in the MUP errors occurred. Up to 50% of errors occurred during the prescribing/ordering phase. 25% to 38% of errors occurred during administration followed by transcription errors and pharmacy dispensing errors.^{3,4}

Avoiding medication errors requires the communication of the right drug, the right dose, the right route, and the right frequency of administration from one health care professional to another. Miscommunications like illegible medication orders, look-alike drug names, and confusion of brand and generic names all can and do lead to medication errors.⁵ When an error is made in the prescribing/ordering phase of the process, it can permeate the MUP and result in an adverse experience for the patient. Because of the prevalence of errors during the prescribing/ordering phase of the MUP, much attention has been given to instituting new practices for prescribing, such as computerized physician order entry (CPOE). One study showed that in the hospital setting, CPOE decreased serious medication errors by 55% and potential adverse drug events (ADEs) by 84%.⁶

Computerized systems are defined as computer programs that maintain patient drug profiles and generate

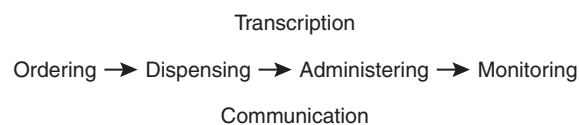


Fig. 27-1 Medication use process.

Physician ordering	39–49%
Nursing administration	26–38%
Transcription	11–12%
Pharmacy dispensing	11–14%

Data from D.W. Bates, D.L. Boyle, N. Laird, et al., *Incidence of Adverse Drug Events and Potential Adverse Drug Events*, 274 J.A.M.A. 29–34 (1995).
L.L. Leape, D.W. Bates, D.J. Cullen, et al., *Systems Analysis of Adverse Drug Events*, 274 J.A.M.A. 35–43 (1995).

Table 27-1 Occurrence of medication errors in studies of hospitalized patients

prescription-fill or dispensing lists. They may also interface with laboratory and other hospital departments. Computerization assists in the initial monitoring of a patient's drug therapy and decreases the chance of drug interactions. Most of the systems used today have built-in programs to detect potential drug interactions. Computerization also decreases the likelihood of drug sensitivities (allergies) going unnoticed, the chance of therapeutic duplications of medications, warn of high dose or low dose alerts, and some include drug disease contraindications. All these enhancements improve medication safety and documentation.

For those hospitals that do not have the resources to purchase expensive computer programs, there are some basic risk management teachings that can be employed to decrease the likelihood of a prescribing error in a "paper-based" prescribing system. For example, when writing a medication order or prescription for an integer or whole number dosage, NEVER use a trailing zero. If the decimal point is lost during transcription, a 10-fold dosing error can occur. The correct procedure is to write 1 mg, not 1.0 mg. On the other hand, when writing for a decimal amount, ALWAYS use a leading zero. For example, Lanoxin 0.250 mg daily. Notice that the word "daily" has been used rather than the abbreviation "qd," which could be mistaken for qid (four times per day) or qod (every other day). The mnemonic to remember is, ALWAYS lead and NEVER follow.

In addition to poor handwriting, legibly written prescriptions can still be misinterpreted if the instructions are ambiguous. Several years ago, the unnecessary death of health reporter Betsy Lehman at a prestigious Boston cancer treatment center made front-page news when she and a second patient both received fatal overdoses of cyclophosphamide, which had been prescribed (by a resident) as part of an experimental protocol to determine if cimetidine could augment the tumor-killing effects of cyclophosphamide in the treatment of breast cancer. According to the IOM report that was cited in an ECRI publication,⁷ the cyclophosphamide order was written "4 g/sq m over four days." Did this mean 4 g/sq m per day or 1 g/sq m per day for 4 days? Unfortunately, it meant 1 g/sq m per day for 4 days, but the full 4 grams/sq m were given in one day. Allegedly, the error was discovered by a Drug Utilization Review (DUR) clerk, who noticed that the price charged to the patient's bill was four times the cost of

a single dose. "Over four days" is too ambiguous. The order should have been written, "1 gram/sq m for 4 days," and should have been reviewed or countersigned by the attending. Making up your own "directions" is truly a prescription for error.

SYSTEM ERRORS

"System errors" is one of the new "buzz words" for describing errors in the MUP that support error-prone practices rather than practices that cannot lead to or do not support errors. In his 1995 article, Leape and coauthors described 13 system errors which were identified as "proximal causes" of medication errors.⁸ These system errors are summarized in Table 27-2. Of the 13 "proximal causes" identified by Leape et al., the failure to provide prescribers with knowledge about drugs accounted for 29% of errors and systems failures to provide physicians with critical information about the patient (e.g., laboratory test results) were associated with 18% of errors. These two categories alone led to 47% of errors, including drug-drug interactions, overdosing patients with diminished renal function, and prescribing drugs to which the patients were allergic.

A recently settled case dramatically describes a systems failure resulting in significant injury. This case involves a patient who received intrathecal vincristine. He did not die, but was permanently paralyzed as a result of this medical error. This case makes for a good study of systems design, of the value of systems, and of what happens when the system breaks down (i.e., when the system is not followed). The patient, a 69-year-old farmer, was scheduled to complete a successful methotrexate/vincristine treatment for lymphoma at a major university medical center. His prognosis was good. One fateful day in May 2000, he arrived at the oncology clinic for his scheduled methotrexate intrathecal and vincristine intravenous treatment. Because the intrathecal injection must be injected under guided fluoroscopy, the oncologist had reserved a radiology suite. No nurse was available to accompany or assist the oncologist who was to administer the injection. The oncologist, not wanting to miss the appointment, stopped at the clinic pharmacy and asked the pharmacist for the "methotrexate and flush (preservative-free NaCl)." The syringes for both the vincristine IV and the methotrexate intrathecal had already been prepared. The staff pharmacist on duty in the clinic pharmacy asked the oncologist, "Would you like the complete order?" The oncologist confirmed, and the pharmacist proceeded to place both the vincristine and the methotrexate syringes in the container, which the oncologist then took to the radiology suite. There the oncologist injected what he knew was methotrexate, followed by the vincristine syringe (which he assumed was preservative-free NaCl).

The patient was taken back to the clinic, where, he believed, he would receive the intravenous vincristine. But the vincristine could not be found. A call to the pharmacy led to the discovery that the vincristine had been given to the oncologist who immediately went to radiology and retrieved the discarded syringes from the sharps container. To his horror, he realized that the vincristine had mistakenly been administered intrathecally in place of the saline flush. An emergency spinal-fluid dialysis/replacement was undertaken, saving the patient's life. Sadly, the patient was left completely paralyzed below the nipple line of his body. The oncologist, devastated over the event, quickly settled with the patient for \$500,000, and took one year off of practice.

Continued

274 Medication Errors

The system failed in a number of ways. Had the system been followed, this accident probably never would have occurred at all. First off, a nurse should have accompanied the oncologist, who, while engaged in a delicate intrathecal injection, did not read the label of the syringe he was administering. Next, although the pharmacy department had a policy in place for utilizing the vincristine manufacturer's (Eli Lilly and Company, Indianapolis, Ind.) syringe label, which read "FATAL IF GIVEN INTRATHECALLY. FOR INTRAVENOUS USE ONLY," and the red-bordered syringe overwrap that warned "FATAL IF GIVEN INTRATHECALLY. FOR IV USE ONLY. DO NOT REMOVE COVERING UNTIL MOMENT OF INJECTION," the oncology clinic pharmacy manager decided that these were unnecessary for adult patients, because the oncology clinic staff was competent and well informed. The staff pharmacist, who knew about the policy in place in the main hospital's sterile-products-compounding room, followed this "unofficial" exemption. That same staff pharmacist, given a verbal order for the "methotrexate and the flush," gave both the methotrexate and the vincristine, thereby violating another system rule, namely, never to place both the methotrexate and the vincristine in the same container. Since many staff pharmacists rotated through the oncology- clinic pharmacy, it was common knowledge that the precautionary syringe label and overwrap were not being used.

A lawsuit was brought against the university hospital, the staff pharmacist, the oncology clinic pharmacy manager, and the director of pharmacy. The lawsuit alleged that the "Hospital and its employees failed to properly promulgate and enforce appropriate policies, procedures and protocols relating to the ordering, packaging, delivery, dispensing, and administration of vincristine; that the Hospital and its employees failed to properly train and supervise employees, and that those failures were substantial factors in causing the plaintiff's injuries and damages." The lawyers for the hospital and the pharmacists argued that it was the oncologist who was to blame, and that the pharmacists and the university were not negligent. While it was recognized that the oncologist was (admittedly) negligent, an overriding theme of the litigation was that this was a systems failure—that if adequate systems controls had been in place and enforced, the accident would not have happened.

This was an unnecessary error, an error that should not have happened. After protracted mediation and settlement negotiations, an additional \$1.6 million was added to the settlement package—thus providing a \$2.1 million settlement, which would almost cover all of the future medical expenses and economic losses.

1. Lack of knowledge about the drug
2. Lack of information about the patient
3. Rule violations
4. Slips and memory lapses
5. Transcription errors
6. Faulty drug identification
7. Faulty interaction with other services
8. Dosing errors
9. Infusion pump/Parenteral delivery error
10. Inadequate monitoring
11. Drug stocking or delivery problem
12. Preparation error
13. Lack of standardization

From L.L. Leape, D.W. Bates, D.J. Cullen, et al, *Systems Analysis of Adverse Drug Events*, 274 J.A.M.A. 35-43 (1995).

Table 27-2 "Proximal causes" of medication errors

Advances such as electronic medical records and reconciling medication use can be helpful in supplying information about the patient's allergies and pathophysiological status, but will not provide the physician with knowledge about the medications he or she is prescribing. Updates on adverse effects of medications, precautions, and contraindications are best obtained from the product labeling or authoritative compendia like the Drug Information text of the American Hospital Formulary Service.

WHICH DRUGS ARE MOST OFTEN INVOLVED IN MEDICATION ERRORS?

"High-risk" drugs are those that have a low "therapeutic index," or are intrinsically toxic. The therapeutic index is defined as the ratio of the toxic dose to the therapeutic dose. Such low therapeutic index drugs provide little margin for overdose. Drugs that are intrinsically toxic include narcotics, anticoagulants, digitalis, and chemotherapy. Table 27-3 provides a list of common "high-risk" drugs, based on their pharmacological properties. One such "high-risk" drug class is the opiate drug class—morphine and its cogeners.

An acute morphine toxicity was alleged as the cause of death of the patient in the following case. A 49-year-old patient was being treated for chronic back pain. He had been given morphine by a nurse practitioner. He called the nurse practitioner to let her know that the medication was not working; she allegedly told him that a mistake had been made in that she had given him the wrong dosage, having switched it for another patient's. She claimed that his dosage should have been stronger. She increased the dosage and told him to take it another 24 hours. Two days later he was acting strangely, jerking around, seeing purple, and was incoherent. The patient was immediately transported to the Northeast Texas Healthcare System Emergency Room where he was pronounced dead.

The autopsy report stated the cause for death was "acute morphine intoxication." The plaintiffs claimed that the nurse overdosed the decedent on morphine. The plaintiffs alleged that the amount of morphine prescribed by the nurse practitioner was 22 times greater than the clinically accepted dosage for postoperative pain. The defendant argued that the nurse prescribed morphine authorized by a doctor and it was to be taken every few hours as needed. The defendants denied that the decedent took the medication as prescribed. They also denied that the increased amount of morphine was a lethal dose. This action settled for \$595,000.⁹

Characteristic	Prototypes
Low therapeutic index	Digoxin, anticoagulants
Inherent undesirable effect(s)	Steroids, chemo
Class of drugs that shares toxicity	NSAIDs, ACEIs
Narcotics/PCA	Morphine, all
Newly-approved drugs	Temofloxacin
"Off-label" uses of drugs	Fen-Phen
Pharmacokinetic drug interactions	SSRIs
Direct-to-consumer promoted	Add-a-med

E1: Au, Chemotherapy?

E2: Au, "all" What?

Table 27-3 Identifying high-risk drugs

Opiates/PCA
 Concentrated solutions of KCl and potassium phosphate
 IV anticoagulants (heparin)
 NaCl solutions above 0.9%
 JCAHO, Issue 11, Nov. 19, 1999.

E3: Au, supply
 complete source

Table 27-4 High-risk drugs reported to JCAHO's Sentinel Event alert Insulin

Another classification of "high-risk" drugs has been compiled by the JCAHO from its Sentinel Event reporting system. Drugs reported to JCAHO due to serious, unexpected adverse reactions are summarized in Table 27-4. Even though the original list was compiled in 1999, the same drugs have continued to be problematic for the past six years. This fact in itself certainly demonstrates the failure of educators, regulators, and legislators to effectively rectify the problems associated with getting information about drugs to the prescriber.

Another high-risk class includes Coumadin and heparin, both anticoagulants. The following is a case report related to heparin:

A 53-year-old man entered the hospital for a femoral bypass surgery. Before his surgical procedure, an inadequate preoperative cardiac workup was performed. Twenty hours after the uneventful surgery, the patient's hemoglobin and hematocrit were low, indicative for possible bleeding. After the surgery, the doctor ordered 7500 units of heparin to be administered over a 24-hour period, or 2500 units every 8 hours continuously. One hour after the order was written, the nursing staff misread the instructions. Instead of administering 2500 units of heparin, they administered 25,000 units of heparin. This caused the patient to continuously bleed, causing his urine output to decline to zero and his heart rate to increase to over 130.

Consultation with a nephrologist and cardiologist was ordered, to see if they could determine the cause of the continuing abdominal pain and the renal failure. At no time did the doctor believe that his orders were not followed with respect to heparin administration. Finally, about 8 hours after the first heparin infusion, the patient was taken back to surgery for an exploratory laparotomy. However, a nurse again prepared him with an additional (negligently misinterpreted) 25,000 units of heparin. Profound and serious bleeding was apparent, but the physician team had no idea what was causing the bleeding. The patient died from a coronary thrombus.

The plaintiff claimed that the cause of death was the failure to adequately perform a preoperative cardiac workup, as well as the negligent administration of toxic levels of heparin. The defendant hospital admitted liability regarding the actions of the nurse but denied that the actions of the nurse had anything to do with the patient's death. The matter settled for \$2.5 million after the jury was selected.¹⁰

An additional anticoagulant case report involving Coumadin (warfarin) is presented:

A complex and confusing order for Coumadin was a factor in a patient's stroke. The patient was hospitalized for heart valve replacement. Her attending physician prescribed 3 mg daily of Coumadin. Because the drug is not available in 1 mg tablets, the doctor prescribed a "net-three" dosage, alternating 2 mg one day with 4 mg the next. After discharge the patient was transferred to a rehabilitation center with a regimen of medications that included the 3 mg dosage of Coumadin. When the doctor wrote the transfer order, he prescribed the net-three dosage on a five-day schedule showing 2 mg one day. He intended for the patient to take Coumadin indefinitely, but the medical director stopped giving the Coumadin after five days.

When the patient was sent home two and a half weeks later, her daughter noticed that Coumadin was not on her medication list and called the doctor, who directed that she begin taking the drug immediately. She did, but suffered a severe stroke the next morning. After the stroke, she needed assistance to walk, was rendered incontinent, did not recognize her grandchildren, and underwent a personality change that made her combative at times. She died of unrelated causes two years later. The jury awarded a verdict of \$850,000.¹¹

Antineoplastics always will occupy the high-risk Sentinel list, not because of the inherent toxicity associated with these cancer chemotherapy drugs, for it is extremely rare for litigation to arise following routine chemotherapy, despite frequent devastating toxicity associated with chemotherapy. Litigation, however, arises when mistakes are made, such as the wrong dose, frequency, or route of administration, often with devastating results. The following case report is an example:

A patient with esophageal cancer was receiving his second round of chemotherapy via a portable infusion pump, which was supposed to deliver the medication over five days at a small continuous rate. Tragically, the nurse programmed the pump to deliver the five-day dose in a five-hour period. After the overdose, the clinic assured the patient that he would be "okay," even though it was probable that he would not survive once his immune system was severely compromised. The patient died suddenly when his immune system crashed nine days later, without having a chance to say goodbye or get his affairs in order. The jury awarded \$3,022,000.¹²

HOW HAS MODERN RESEARCH IMPROVED THERAPEUTICS AND REDUCED DRUG-RELATED MORBIDITY?

Contemporary research into the metabolism of drugs by the cytochrome P-450 (CYP) enzymes of the liver has given rise to a more complete understanding of the genetic differences among individuals and the related variability in the capacity of patients to metabolize drugs to various degrees. In past decades, pharmacologists talked about "slow" and "fast" acetylators of hydralazine and procainamide and the bimodal distribution of drug-induced

276 Medication Errors

lupus-like symptoms associated with each genetic phenotype. It was determined that slow acetylators of hydralazine and procainamide were more likely to develop the lupus-like syndrome than fast acetylators,¹³ thus indicating that the parent compounds, and not the acetylated metabolites, were responsible for producing the syndrome.

Today, instead of discussing the CYP microsomal enzyme system as a whole, researchers in pharmacogenetics have studied how the interindividual variations in the DNA sequence of a gene responsible for producing a protein that is involved in the absorption, transport, or metabolism of a drug affect drug action (pharmacodynamics).¹⁴ More than 27 families of CYP enzymes have been identified, but only three families, (CYP1, CYP2, and CYP3) are believed to be involved with the vast majority of human drug metabolism.¹⁵ These CYP families share >40% of the amino acids in their primary sequence and can be further subdivided into subfamilies that share >55% of their amino acid sequence.¹⁶ Often, two or more enzymes catalyze the metabolism of a drug, but clearly the most influential families are the CYP3A, of which the CYP3A4 is involved in the metabolism of over 50% of all drugs and the CYP2D6 is involved in the metabolism of approximately 25% of drugs.¹⁷ However, variations in the expression of the CYP2C9 subfamily are responsible for the great variability in the anticoagulant effect of warfarin.¹⁸ Also, the CYP2E1 enzyme, which contributes to the metabolism of ethanol in frequent drinkers, can be induced by ethanol, Phenobarbital, and phenytoin, which can increase the formation of *n*-acetyl-*p*-benzoquinoneimine (NAPQI), the hepatotoxic metabolite of acetaminophen, and increase the likelihood of liver failure from moderate doses of acetaminophen.^{19,20} Nutritional factors involving the ingestion of the sulfur-containing amino acid cysteine, which contributes to endogenous glutathione production, are also significant factors, especially in children, who rely more on sulfation than conjugation with glucuronic acid. Children under 12 years of age should never receive adult-strength acetaminophen products.

With the application of the Human Genome Project to clinical practice, the science of pharmacogenomics has the potential to determine how alterations in gene expression influence both drug discovery and pharmacogenetic polymorphism.^{14,21} Some researchers predict that bedside testing for a patient's capacity to metabolize a drug will become a standard part of clinical practice within the next two decades.²² Elucidation of a patient's particular genomic composition can greatly decrease drug-induced disease and provide critical information not only on interindividual pharmacogenetic polymorphism, but also on interracial differences in drug-metabolizing capacities.

Another application of pharmacogenetics and pharmacogenomics will be their effect on public policy issues regarding the removal of drugs from the marketplace due to drug-drug interactions. Within the past two decades, several drugs have been removed from the marketplace because of intolerable side effects that were caused by drug-drug interactions. Two of the agents best known to

millions of Americans were Seldane[®] (terfenadine) and Hismanal[®] (astemizole), the first two nonsedating antihistamines. These agents were removed from the market despite the fact that the Food and Drug Administration (FDA) required the manufacturers to include "Black Box" warnings in their product labeling warning about potential cardiotoxic effects such as prolongation of the QT interval due to inhibition of the CYP3A4 pathway by "conazole" antifungals and macrolide antibiotics.²³ A similar set of circumstances led to the same effect on the QT interval with the gastrointestinal motility enhancing agent cisapride (Propulsid[®]). According to one study, the manufacturer withdrew this drug from the market in March 2000 because the inclusion of a "Black Box" warning and the issuance of a "Dear Doctor" letter to 800,000 health care professionals failed to modify physician prescribing practices sufficiently to reduce contraindicated use of cisapride and further cardiotoxic events. The authors also commented on the need to find more effective ways to provide prescribers with critical new safety information on the proper use of drugs.²⁴

According to the FDA:

The inability of the FDA to effectively warn health care providers and patients about drug interactions and our inability to translate existing knowledge into changes in prescribing have resulted in huge economic consequences for the pharmaceutical industry and the loss from the marketplace of effective drugs, including terfenadine, mibefradil, astemizole, and cisapride.²⁵

IMPLICATIONS OF PHARMACOGENETICS AND PHARMACOGENOMICS ON MEDICAL NEGLIGENCE

Recognizing that the standard of care for acceptable medical practice is to exercise that degree of care which a reasonably prudent practitioner would exercise under the same or similar circumstances, there can be no doubt that physicians, pharmacists, and nurses all must consult drug labeling and/or learned treatises that contain warnings, precautions, and contraindications to the use of medications they prescribe, dispense, or administer. The information is available, and the likelihood for morbidity and death are reasonably foreseeable. Failure to recognize the potential adverse effects, and to take reasonable precautions to guard against preventable errors, is a deviation from the standard of care.

Moreover, it is time to recognize that health care is a team activity. Practicing medicine, nursing, and pharmacy is too complicated for health care professionals to be able to carry all the required information in their heads. Electronic and computerized systems can help, but first, all health care professionals must acknowledge that a problem exists. Today's philosophy is to improve faulty systems through root cause analysis and redesign. Computerized physician order entry (CPOE), bar coding

drugs and patient identification bands, and hiring clinical pharmacists to make rounds with physicians can decrease costly errors. Every preventable medication error costs almost \$5000 in extended or rehospitalization expenses. The data are clear—preventing medication errors will pay for itself. One PharmD in one unit recommended changes in medication orders to physicians and saved a hospital a projected \$270,000 that year.²⁶ Moreover, fewer errors will be committed, you will provide a higher quality of care, patients will be safer and better served, and less litigation will ensue. There is no question that the price of quality improvement is less than the costs of medication errors.

Endnotes

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3. D.W. Bates, D.L. Boyle, N. Laird, et al., *Incidence of Adverse Drug Events and Potential Adverse Drug Events*, 274 J.A.M.A. 29–34 (1995).
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