

1

What is Pharmacoepidemiology?

Edited by:

BRIAN L. STROM

University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania, USA.

A desire to take medicine is, perhaps, the great feature which distinguishes man from other animals.

Sir William Osler, 1891

In recent decades, modern medicine has been blessed with a pharmaceutical armamentarium that is much more powerful than what it had before. Although this has given health care providers the ability to provide better medical care for their patients, it has also resulted in the ability to do much greater harm. It has also generated an enormous number of product liability suits against pharmaceutical manufacturers, some appropriate and others inappropriate. In fact, the history of drug regulation parallels the history of major adverse drug reaction “disasters.” Each change in pharmaceutical law was a political reaction to an epidemic of adverse drug reactions. Recent data suggest that perhaps 100 000 Americans die each year from adverse drug reactions (ADRs), and 1.5 million US hospitalizations each year result from ADRs; yet, 20–70% of ADRs may be preventable. The harm that drugs can cause has also led to the development of the field of pharmacoepidemiology, which is the focus of this book. More recently, the field has expanded its focus to include many issues other than adverse reactions, as well.

To clarify what is, and what is not, included within the discipline of pharmacoepidemiology, this chapter will

begin by defining pharmacoepidemiology, differentiating it from other related fields. The history of drug regulation will then be briefly and selectively reviewed, focusing on the US experience as an example, demonstrating how it has led to the development of this new field. Next, the current regulatory process for the approval of new drugs will be reviewed, in order to place the use of pharmacoepidemiology and postmarketing drug surveillance into proper perspective. Finally, the potential scientific and clinical contributions of pharmacoepidemiology will be discussed.

DEFINITION OF PHARMACOEPIDEMOLOGY

Pharmacoepidemiology is the study of the use of and the effects of drugs in large numbers of people. The term pharmacoepidemiology obviously contains two components: “pharmaco” and “epidemiology.” In order to better appreciate and understand what is and what is not included in this field, it is useful to compare its scope to that of other related fields. The scope of pharmacoepidemiology will first be compared to that of clinical pharmacology, and then to that of epidemiology.

PHARMACOEPIDEMOLOGY VERSUS CLINICAL PHARMACOLOGY

Pharmacology is the study of the effects of drugs. *Clinical pharmacology* is the study of the effects of drugs in humans (see also Chapter 4). Pharmacoepidemiology obviously can be considered, therefore, to fall within clinical pharmacology. In attempting to optimize the use of drugs, one central principle of clinical pharmacology is that therapy should be individualized, or tailored to the needs of the specific patient at hand. This individualization of therapy requires the determination of a risk/benefit ratio specific to the patient at hand. Doing so requires a prescriber to be aware of the potential beneficial and harmful effects of the drug in question and to know how elements of the patient's clinical status might modify the probability of a good therapeutic outcome. For example, consider a patient with a serious infection, serious liver impairment, and mild impairment of his or her renal function. In considering whether to use gentamicin to treat the infection, it is not sufficient to know that gentamicin has a small probability of causing renal disease. A good clinician should realize that a patient who has impaired liver function is at a greater risk of suffering from this adverse effect than one with normal liver function. Pharmacoepidemiology can be useful in providing information about the beneficial and harmful effects of any drug, thus permitting a better assessment of the risk/benefit balance for the use of any particular drug in any particular patient.

Clinical pharmacology is traditionally divided into two basic areas: pharmacokinetics and pharmacodynamics. *Pharmacokinetics* is the study of the relationship between the dose administered of a drug and the serum or blood level achieved. It deals with drug absorption, distribution, metabolism, and excretion. *Pharmacodynamics* is the study of the relationship between drug level and drug effect. Together, these two fields allow one to predict the effect one might observe in a patient from administering a certain drug regimen. Pharmacoepidemiology encompasses elements of both of these fields, exploring the effects achieved by administering a drug regimen. It does not normally involve or require the measurement of drug levels. However, pharmacoepidemiology can be used to shed light on the pharmacokinetics of a drug, such as exploring whether aminophylline is more likely to cause nausea when administered to a patient simultaneously taking cimetidine. However, to date this is a relatively unusual application of the field.

Specifically, the field of pharmacoepidemiology has primarily concerned itself with the study of adverse drug effects. Adverse reactions have traditionally been separated into those which are the result of an exaggerated but otherwise usual pharmacological effect of the drug, sometimes

called *Type A reactions*, versus those which are aberrant effects, so-called *Type B reactions*. Type A reactions tend to be common, dose-related, predictable, and less serious. They can usually be treated by simply reducing the dose of the drug. They tend to occur in individuals who have one of three characteristics. First, the individuals may have received more of a drug than is customarily required. Second, they may have received a conventional amount of the drug, but they may metabolize or excrete the drug unusually slowly, leading to drug levels that are too high. Third, they may have normal drug levels, but for some reason are overly sensitive to them.

In contrast, Type B reactions tend to be uncommon, not related to dose, unpredictable, and potentially more serious. They usually require cessation of the drug. They may be due to what are known as hypersensitivity reactions or immunologic reactions. Alternatively, Type B reactions may be some other idiosyncratic reaction to the drug, either due to some inherited susceptibility (e.g., glucose-6-phosphate dehydrogenase deficiency) or due to some other mechanism. Regardless, Type B reactions are the more difficult to predict or even detect, and represent the major focus of many pharmacoepidemiology studies of adverse drug reactions.

The usual approach to studying adverse drug reactions has been the collection of spontaneous reports of drug-related morbidity or mortality (see Chapters 7 and 8). However, determining causation in case reports of adverse reactions can be problematic (see Chapter 17), as can attempts to compare the effects of drugs in the same class. This has led academic investigators, industry, the Food and Drug Administration (FDA), and the legal community to turn to the field of epidemiology. Specifically, *studies of adverse effects* have been supplemented with *studies of adverse events*. In the former, investigators examine case reports of purported adverse drug reactions and attempt to make a subjective clinical judgment on an *individual* basis about whether the adverse outcome was actually caused by the antecedent drug exposure. In the latter, controlled studies are performed examining whether the adverse outcome under study occurs more often in an exposed *population* than in an unexposed population. This marriage of the fields of clinical pharmacology and epidemiology has resulted in the development of a new field: pharmacoepidemiology.

PHARMACOEPIDEMOLOGY VERSUS EPIDEMIOLOGY

Epidemiology is the study of the distribution and determinants of diseases in populations (see Chapter 2). Since pharmacoepidemiology is the study of the use of and effects

of drugs in large numbers of people, it obviously falls within epidemiology as well. Epidemiology is also traditionally subdivided into two basic areas. The field began as the study of infectious diseases in large populations, i.e., epidemics. More recently, it has also been concerned with the study of chronic diseases. The field of pharmacoepidemiology uses the techniques of chronic disease epidemiology to study the use of and the effects of drugs. Although application of the methods of pharmacoepidemiology can be useful in performing the clinical trials of drugs that are performed before marketing (see Chapter 20), the major application of these principles is after drug marketing. This has primarily been in the context of postmarketing drug surveillance, although in recent years the interests of pharmacoepidemiologists have broadened considerably.

Thus, pharmacoepidemiology is a relatively new applied field, bridging between clinical pharmacology and epidemiology. From clinical pharmacology, pharmacoepidemiology borrows its focus of inquiry. From epidemiology, pharmacoepidemiology borrows its methods of inquiry. In other words, it applies the methods of epidemiology to the content area of clinical pharmacology. In the process, multiple special logistical approaches have been developed and multiple special methodologic issues have arisen. These are the primary foci of this book.

HISTORICAL BACKGROUND

The history of drug regulation in the US is similar to that in most developed countries, and reflects the growing involvement of governments in attempting to assure that only safe and effective drug products were available and that appropriate manufacturing and marketing practices were used. The initial US law, the Pure Food and Drug Act, was passed in 1906, in response to excessive adulteration and misbranding of the food and drugs available at that time. There were no restrictions on sales or requirements for proof of the efficacy or safety of marketed drugs. Rather, the law simply gave the Federal Government the power to remove from the market any product that was adulterated or misbranded. The burden of proof was on the Federal Government.

In 1937, over 100 people died from renal failure as a result of the marketing by the Massengill Company of elixir of sulfanilimide dissolved in diethylene glycol. In response, the Food, Drug, and Cosmetic Act was passed in 1938. Preclinical toxicity testing was required for the first time. In addition, manufacturers were required to gather clinical data about drug safety and to submit these data to the FDA before drug marketing. The FDA had 60 days to object to

marketing or else it would proceed. No proof of efficacy was required.

Little attention was paid to adverse drug reactions until the early 1950s, when it was discovered that chloramphenicol could cause aplastic anemia. In 1952, the first textbook of adverse drug reactions was published. In the same year, the AMA Council on Pharmacy and Chemistry established the first official registry of adverse drug effects, to collect cases of drug-induced blood dyscrasias. In 1960, the FDA began to collect reports of adverse drug reactions and sponsored new hospital-based drug monitoring programs. The Johns Hopkins Hospital and the Boston Collaborative Drug Surveillance Program developed the use of in-hospital monitors to perform cohort studies to explore the short-term effects of drugs used in hospitals (see Chapter 27). This approach was later to be transported to the University of Florida–Shands Teaching Hospital as well.

In the winter of 1961, the world experienced the infamous “thalidomide disaster.” Thalidomide was marketed as a mild hypnotic, and had no obvious advantage over other drugs in its class. Shortly after its marketing, a dramatic increase was seen in the frequency of a previously rare birth defect, phocomelia—the absence of limbs or parts of limbs, sometimes with the presence instead of flippers. Epidemiologic studies established its cause to be *in utero* exposure to thalidomide. In the United Kingdom, this resulted in the establishment in 1968 of the Committee on Safety of Medicines. Later, the World Health Organization established a bureau to collect and collate information from this and other similar national drug monitoring organizations (see Chapter 8).

The US had never permitted the marketing of thalidomide and, so, was fortunately spared this epidemic. However, the thalidomide disaster was so dramatic that it resulted in regulatory change in the US as well. Specifically, in 1962 the Kefauver–Harris Amendments were passed. These amendments strengthened the requirements for proof of drug safety, requiring extensive preclinical pharmacological and toxicological testing before a drug could be tested in humans. The data from these studies were required to be submitted to the FDA in an Investigational New Drug Application (IND) before clinical studies could begin. Three explicit phases of clinical testing were defined, which are described in more detail below. In addition, a new requirement was added to the clinical testing, for “substantial evidence that the drug will have the effect it purports or is represented to have.” “Substantial evidence” was defined as “adequate and well-controlled investigations, including clinical investigations.” Functionally, this has generally been interpreted as requiring randomized clinical trials to

document drug efficacy before marketing. This new procedure also delayed drug marketing until the FDA explicitly gave approval. With some modifications, these are the requirements still in place in the US today. In addition, the amendments required the review of all drugs approved between 1938 and 1962, to determine if they too were efficacious. The resulting Drug Efficacy Study Implementation (DESI) process, conducted by the National Academy of Sciences' National Research Council with support from a contract from the FDA, was not completed until relatively recently, and resulted in the removal from the US market of many ineffective drugs and drug combinations. The result of all these changes was a great prolongation of the approval process, with attendant increases in the cost of drug development, the so-called drug lag. However, the drugs that are marketed are presumably much safer and more effective.

The mid-1960s also saw the publication of a series of drug utilization studies. These studies provided the first descriptive information on how physicians use drugs, and began a series of investigations of the frequency and determinants of poor prescribing (see also Chapter 27).

With all of these developments, the 1960s can be thought to have marked the beginning of the field of pharmacoepidemiology.

Despite the more stringent process for drug regulation, the late 1960s, 1970s, 1980s, and especially the 1990s and 2000s have seen a series of major adverse drug reactions. Subacute myelo-optic-neuropathy (SMON) was found to be caused by clioquinol, a drug marketed in the early 1930s but not discovered to cause this severe neurological reaction until 1970. In the 1970s, clear cell adenocarcinoma of the cervix and vagina and other genital malformations were found to be due to *in utero* exposure to diethylstilbestrol two decades earlier. The mid-1970s saw the discovery of the oculomucocutaneous syndrome caused by practolol, five years after drug marketing. In part in response to concerns about adverse drug effects, the early 1970s saw the development of the Drug Epidemiology Unit, now the Slone Epidemiology Center, which extended the hospital-based approach of the Boston Collaborative Drug Surveillance Program (Chapter 27) by collecting lifetime drug exposure histories from hospitalized patients and using these to perform hospital-based case-control studies (see Chapter 9). The year 1976 saw the formation of the Joint Commission on Prescription Drug Use, an interdisciplinary committee of experts charged with reviewing the state of the art of pharmacoepidemiology at that time, as well as providing recommendations for the future. The Computerized Online Medicaid Analysis and Surveillance System was first developed in 1977, using Medicaid billing data to perform

pharmacoepidemiology studies (see Chapters 11 and 12). The Drug Surveillance Research Unit, now called the Drug Safety Research Trust, was developed in the United Kingdom in 1980, with its innovative system of Prescription Event Monitoring (see Chapter 10). Each of these represented major contributions to the field of pharmacoepidemiology. These and newer approaches are reviewed in Section II of this book.

In 1980, the drug ticrynafen was noted to cause deaths from liver disease. In 1982, benoxaprofen was noted to do the same. Subsequently, the use of zomepirac, another nonsteroidal anti-inflammatory drug, was noted to be associated with an increased risk of anaphylactoid reactions. Serious blood dyscrasias were linked to phenylbutazone. Small intestinal perforations were noted to be caused by a particular slow release formulation of indomethacin. Bendectin[®], a combination product indicated to treat nausea and vomiting in pregnancy, was removed from the market because of litigation claiming it was a teratogen, despite the absence of valid scientific evidence to justify this claim (see Chapter 27). Acute flank pain and reversible acute renal failure were noted to be caused by suprofen. Isotretinoin was almost removed from the US market because of the birth defects it causes. The eosinophilia-myalgia syndrome was linked to a particular brand of L-tryptophan. Triazolam, thought by the Netherlands in 1979 to be subject to a disproportionate number of central nervous system side effects, was discovered by the rest of the world to be problematic in the early 1990s. Silicone breast implants, inserted by the millions in the US for cosmetic purposes, were accused of causing cancer, rheumatologic disease, and many other problems, and was restricted from use except for breast reconstruction after mastectomy. Human insulin was marketed as one of the first of the new biotechnology drugs, but soon thereafter was accused of causing a disproportionate amount of hypoglycemia. Fluoxetine was marketed as a major new important and commercially successful psychiatric product, but then lost a large part of its market due to accusations about its association with suicidal ideation. An epidemic of deaths from asthma in New Zealand was traced to fenoterol, and later data suggested that similar, although smaller, risks might be present with other beta-agonist inhalers. The possibility was raised of cancer from depot-medroxyprogesterone, resulting in initial refusal to allow its marketing for contraception in the US, multiple studies, and ultimate approval. Arrhythmias were linked to the use of the antihistamines terfenadine and astemizole. Hypertension, seizures, and strokes were noted from postpartum use of bromocriptine. Multiple different adverse reactions were linked to temafloxacin. Other examples include liver

toxicity from amoxicillin-clavulanic acid; liver toxicity from bromfenac; cancer, myocardial infarction, and gastrointestinal bleeding from calcium channel blockers; arrhythmias with cisapride interactions; primary pulmonary hypertension and cardiac valvular disease from dexfenfluramine and fenfluramine; gastrointestinal bleeding, postoperative bleeding, deaths, and many other adverse reactions associated with ketorolac; multiple drug interactions with mibefradil; thrombosis from newer oral contraceptives; myocardial infarction from sildenafil; seizures with tramadol; anaphylactic reactions from vitamin K; liver toxicity from troglitazone; and intussusception from rotavirus vaccine.

More recently, drug crises have occurred due to allegations of ischemic colitis from alosetron; rhabdomyolysis from cerivastatin; bronchospasm from rapacuronium; torsade de pointes from ziprasidone; hemorrhagic stroke from phenylpropanolamine; arthralgia, myalgia, and neurologic conditions from Lyme vaccine; multiple joint and other symptoms from anthrax vaccine; myocarditis and myocardial infarction from smallpox vaccine; and heart attack and stroke from rofecoxib. Twenty-two different prescription drug products have been removed from the US market since 1980 alone—alosetron (2000), astemizole (1999), benoxaprofen (1982), bromfenac (1998), cerivastatin (2001), cisapride (2000), dexfenfluramine (1997), encainide (1991), fenfluramine (1998), flosequin (1993), grepafloxin (1999), mibefradil (1998), nomifensine (1986), phenylpropanolamine (2000), rapacuronium (2001), rofecoxib (2004), suprofen (1987), terfenadine (1998), temafloxacin (1992), ticrynafen (1980), troglitazone (2000), and zomepirac (1983) (see Chapter 6).

The licensed vaccines against rotavirus and Lyme were also recently withdrawn because of safety concerns (see Chapter 27). Between 1990 and 2004, at least 13 non-cardiac drugs were subject to significant regulatory actions because of cardiac concerns, including astemizole, cisapride, droperidol, grepafloxacin, halofantrine, pimozone, rofecoxib, sertindole, terfenadine, terodiline, thioridazine, vevacetylmethadol, and ziprasidone.

In some of these examples, the drug was never convincingly linked to the adverse reaction. However, many of these discoveries led to the removal of the drug involved from the market. Interestingly, however, this withdrawal was not necessarily performed in all of the different countries in which each drug was marketed. Most of these discoveries have led to litigation, as well, and a few have even led to criminal charges against the pharmaceutical manufacturer and/or some of its employees.

Each of these was a serious but uncommon drug effect, and these and other serious but uncommon drug effects have

led to an accelerated search for new methods to study drug effects in large numbers of patients. This led to a shift from adverse effect studies to adverse event studies.

The 1990s and especially the 2000s have seen another shift in the field, away from its exclusive emphasis on drug utilization and adverse reactions, to the inclusion of other interests as well, such as the use of pharmacoepidemiology to study beneficial drug effects, the application of health economics to the study of drug effects, quality-of-life studies, meta-analysis, etc. These new foci are discussed in more detail in Section III of this book.

Recent years have seen increasing use of these data resources and new methodologies, with continued and even growing concern about adverse reactions. The American Society for Clinical Pharmacology and Therapeutics issued, in 1990, a position paper on the use of purported postmarketing drug surveillance studies for promotional purposes, and the International Society for Pharmacoepidemiology issued, in 1996, Guidelines for Good Epidemiology Practices for Drug, Device, and Vaccine Research in the United States, which was very recently updated. In the late 1990s, pharmacoepidemiologic research has been increasingly hampered by concerns about patient confidentiality (see also Chapter 19).

Organizationally, in the US, the Prescription Drug User Fee Act (PDUFA) of 1992 allowed the US FDA to charge manufacturers a fee for reviewing New Drug Applications. This provided additional resources to the FDA, and greatly accelerated the drug approval process. New rules in the US, and in multiple other countries, now permit direct-to-consumer advertising of prescription drugs. The result is a system where more than 330 new medications were approved by the FDA in the 1990s. Each drug costs \$300–500 million to develop; drug development cost the pharmaceutical industry a total of \$24 billion in 1999 and \$32 billion in 2002.

Yet, funds from the PDUFA of 1992 were initially prohibited from being used for drug safety regulation. In 1998, whereas 1400 FDA employees worked with the drug approval process, only 52 monitored safety; the FDA spent only \$2.4 million in extramural safety research. This has coincided with the growing numbers of drug crises cited above. With the passage of PDUFA III, however, this is markedly changing (see Chapter 6). As another measure of drug safety problems, the FDA's new MedWatch program of collecting spontaneous reports of adverse reactions (see Chapter 7) now issues monthly notifications of label changes, and as of mid-1999, 20–25 safety-related label changes are being made every month. According to a study by the US Government Accounting Office,

51% of approved drugs have serious adverse effects not detected before approval. Further, there is recognition that the initial dose recommended for a newly marketed drug is often incorrect, and needs monitoring and modification after marketing.

Recently, with the publication of the results from the Women's Health Initiative indicating that combination hormone replacement therapy causes an increased risk of myocardial infarction rather than a decreased risk, there has been increased concern about reliance solely on nonexperimental methods to study drug safety after marketing, and we are beginning to see the use of massive randomized clinical trials as part of postmarketing surveillance (see Chapter 20).

There is also increasing recognition that most of the risk from most drugs to most patients occurs from known reactions to old drugs. Yet, nearly all of the efforts by the FDA and other regulatory bodies are devoted to discovering rare unknown risks from new drugs. In response, there is growing concern, in Congress and among the US public at least, that perhaps the FDA is now approving drugs too *fast*. There are also calls for the development of an independent drug safety board, analogous to the National Transportation Safety Board, with a mission much wider than the FDA's regulatory mission, to complement the latter. For example, such a board could investigate drug safety crises such as those cited above, looking for ways to prevent them, and could deal with issues such as improper physician use of drugs, the need for training, and the development of new approaches to the field of pharmacoepidemiology.

As an attempt to address the kinds of questions which until now have not been addressed, the US Agency for Healthcare Research and Quality (AHRQ) has funded seven Centers for Education and Research on Therapeutics (CERTs). Discussed more in Chapter 6, the CERTs program seeks to improve health care and patient safety. It has identified specific roles that include: (a) development and nurturing of public-private partnerships to facilitate research on therapeutics; (b) support and encouragement of research on therapeutics likely to get translated into policy or clinical practice; (c) development of educational modules and dissemination strategies to increase awareness of the benefits and risks of pharmaceuticals; and (d) creation of a national information resource on the safe and effective use of therapeutics. Activities include the conduct of research on therapeutics, specifically exploring new uses of drugs, ways to improve the effective uses of drugs, and risks associated with new uses or combinations of drugs. The CERTs also develop educational modules and materials for disseminating the findings from their research, consistent with

their overarching mission to become a national resource for people seeking information about medical products. The CERTs strive to seek public and private sector cooperation to facilitate these efforts.

Another new initiative closely related to pharmacoepidemiology is the Patient Safety movement. In the Institute of Medicine's report, *To Err is Human: Building a Safer Health System*, the authors note that: (a) "even apparently single events or errors are due most often to the convergence of multiple contributing factors," (b) "preventing errors and improving safety for patients requires a systems approach in order to modify the conditions that contribute to errors," and (c) "the problem is not bad people; the problem is that the system needs to be made safer." In this framework, the concern is not about substandard or negligent care, but rather, is about errors made by even the best trained, brightest, and most competent professional health caregivers and/or patients. From this perspective, the important research questions ask about the conditions under which people make errors, the types of errors being made, and the types of systems that can be put into place to prevent errors altogether when possible. Errors that are not prevented must be identified and corrected efficiently and quickly, before they inflict harm. Turning specifically to medications, from 2.4% to 6.5% of hospitalized patients suffer adverse drug events (ADEs), prolonging hospital stays by 2 days, and increasing costs by \$2000–2600 per patient. Over 7000 US deaths were attributed to medication errors in 1993. Although these estimates have been disputed, the overall importance of reducing these errors has not been questioned. In recognition of this problem, the AHRQ has launched a major new grant program of over 100 projects, with over \$50 million/year of funding. While only a portion of this is dedicated to medication errors, they are clearly a focus of interest and relevance to many. More information is provided in Chapter 27. A recent CERT paper called for a systematic review of the entire drug risk assessment process, perhaps as a study by the US Institute of Medicine. That study is underway, at least in part in response to the circumstances surrounding the withdrawal of rofecoxib.

Finally, another major new initiative of close relevance to pharmacoepidemiology is risk management. There is increasing recognition that the risk/benefit balance of some drugs can only be considered acceptable with active management of their use, to maximize their efficacy and/or minimize their risk. In response, there are many initiatives underway, ranging from new FDA requirements for risk management plans, to a new FDA Drug Safety and

Risk Management Advisory Committee. More information is provided in Chapters 6 and 27.

THE CURRENT DRUG APPROVAL PROCESS

The current drug approval process in the US and most other developed countries includes preclinical animal testing followed by three phases of clinical testing. Phase I testing is usually conducted in just a few normal volunteers, and represents the initial trials of the drug in humans. Phase I trials are generally conducted by clinical pharmacologists, to determine the metabolism of the drug and a safe dosage range in humans, and to exclude any extremely common toxic reactions which are unique to humans.

Phase II testing is also generally conducted by clinical pharmacologists, on a small number of patients who have the target disease. Phase II testing is usually the first time patients are exposed to the drug. Exceptions are drugs that are so toxic that it would not normally be considered ethical to expose healthy individuals to them, like cytotoxic drugs. For these, patients are used for Phase I testing as well. The goals of Phase II testing are to obtain more information on the pharmacokinetics of the drug and on any relatively common adverse reactions, and to obtain initial information on the possible efficacy of the drug. Specifically, Phase II is used to determine the daily dosage and regimen to be tested more rigorously in Phase III.

Phase III testing is performed by clinician–investigators in a much larger number of patients, in order to rigorously evaluate a drug’s efficacy and to provide more information on its toxicity. At least one of the Phase III studies needs to be a randomized clinical trial (see Chapter 2). To meet FDA standards, at least one of the randomized clinical trials usually needs to be conducted in the US. Generally between 500 and 3000 patients are exposed to a drug during Phase III, even if drug efficacy can be demonstrated with much smaller numbers, in order to be able to detect less common adverse reactions. For example, a study including 3000 patients would allow one to be 95% certain of detecting any adverse reactions that occur in at least one exposed patient out of 1000 (see Chapter 2 for a discussion of confidence intervals). At the other extreme, a total of 500 patients would allow one to be 95% certain of detecting any adverse reactions which occur in 6 or more patients out of every 1000 exposed. Adverse reactions which occur less commonly than these are less likely to be detected in these premarketing studies. The sample sizes needed to detect drug effects are discussed in more detail in Chapter 3.

POTENTIAL CONTRIBUTIONS OF PHARMACOEPIDEMOLOGY

The potential contributions of pharmacoepidemiology are only beginning to be realized, as the field is relatively new. However, some contributions are already apparent (see Table 1.1). In fact, since the early 1970s the FDA has required postmarketing research at the time of approval for about one third of drugs. In this section we will first review the potential for pharmacoepidemiology studies to supplement the information available prior to marketing, and then review the new types of information obtainable from postmarketing pharmacoepidemiology studies but not obtainable prior to drug marketing. Finally, we will review the general, and probably most important, potential contributions such studies can make. In each case, the relevant information available from premarketing studies will be briefly examined first, to clarify how postmarketing studies can supplement this information.

SUPPLEMENTARY INFORMATION

Premarketing studies of drug effects are necessarily limited in size. After marketing, nonexperimental epidemiologic studies can be performed, evaluating the effects of drugs administered as part of ongoing medical care. These allow the cost-effective accumulation of much larger numbers of

Table 1.1. Potential contributions of pharmacoepidemiology

-
- | | |
|-----|--|
| (A) | Information which supplements the information available from premarketing studies—better quantitation of the incidence of known adverse and beneficial effects |
| | (a) Higher precision |
| | (b) In patients not studied prior to marketing, e.g., the elderly, children, pregnant women |
| | (c) As modified by other drugs and other illnesses |
| | (d) Relative to other drugs used for the same indication |
| (B) | New types of information not available from premarketing studies |
| | (1) Discovery of previously undetected adverse and beneficial effects |
| | (a) Uncommon effects |
| | (b) Delayed effects |
| | (2) Patterns of drug utilization |
| | (3) The effects of drug overdoses |
| | (4) The economic implications of drug use |
| (C) | General contributions of pharmacoepidemiology |
| | (1) Reassurances about drug safety |
| | (2) Fulfillment of ethical and legal obligations |
-

patients than those studied prior to marketing, resulting in a more precise measurement of the incidence of adverse and beneficial drug effects (see Chapter 3). For example, at the time of drug marketing, prazosin was known to cause a dose-dependent first dose syncope, but the FDA requested the manufacturer to conduct a postmarketing surveillance study in the US to quantitate its incidence more precisely. In recent years, there has even been an attempt, in selected special cases, to release selected critically important drugs more quickly, by taking advantage of the work that can be performed after marketing. Probably the best-known example was zidovudine. As noted above, the increased sample size available after marketing also permits a more precise determination of the correct dose to be used.

Premarketing studies also tend to be very artificial. Important subgroups of patients are not typically included in studies conducted before drug marketing, usually for ethical reasons. Examples include the elderly, children, and pregnant women. Studies of the effects of drugs in these populations generally must await studies conducted after drug marketing.

Additionally, for reasons of statistical efficiency, premarketing clinical trials generally seek subjects who are as homogeneous as possible, in order to reduce unexplained variability in the outcome variables measured and increase the probability of detecting a difference between the study groups, if one truly exists. For these reasons, certain patients are often excluded, including those with other illnesses or those who are receiving other drugs. Postmarketing studies can explore how factors such as other illnesses and other drugs might modify the effects of the drugs, as well as examine the effects of differences in drug regimen, compliance, etc. For example, after marketing, the ophthalmic preparation of timolol was noted to cause many serious episodes of heart block and asthma, resulting in over ten deaths. These effects were not detected prior to marketing, as patients with underlying cardiovascular or respiratory disease were excluded from the premarketing studies.

Finally, to obtain approval to market a drug, a manufacturer needs to evaluate its overall safety and efficacy, but does not need to evaluate its safety and efficacy relative to any other drugs available for the same indication. To the contrary, with the exception of illnesses that could not ethically be treated with placebos, such as serious infections and malignancies, it is generally considered preferable, or even mandatory, to have studies with placebo controls. There are a number of reasons for this preference. First, it is easier to show that a new drug is more effective than a placebo than to show it is more effective than another effective drug. Second, one cannot actually prove that a new

drug is as effective as a standard drug. A study showing a new drug is no worse than another effective drug does not provide assurance that it is better than a placebo; one simply could have failed to detect that it was in fact worse than the standard drug. One could require a demonstration that a new drug is more effective than another effective drug, but this is a standard that does not and should not have to be met. Yet, optimal medical care requires information on the effects of a drug relative to the alternatives available for the same indication. This information must often await studies conducted after drug marketing.

NEW TYPES OF INFORMATION NOT AVAILABLE FROM PREMARKETING STUDIES

As mentioned above, premarketing studies are necessarily limited in size. The additional sample size available in postmarketing studies permits the study of drug effects that may be uncommon, but important, such as drug-induced agranulocytosis.

Premarketing studies are also necessarily limited in time; they must come to an end, or the drug could never be marketed! In contrast, postmarketing studies permit the study of delayed drug effects, such as the unusual clear cell adenocarcinoma of the vagina and cervix, which occurred two decades later in women exposed *in utero* to diethylstilbestrol.

The patterns of physician prescribing and patient drug utilization often cannot be predicted prior to marketing, despite pharmaceutical manufacturers' best attempts to predict in planning for drug marketing. Studies of how a drug is actually being used, and determinants of changes in these usage patterns, can only be performed after drug marketing (see Chapter 27).

In most cases, premarketing studies are performed using selected patients who are closely observed. Rarely are there any significant overdoses in this population. Thus, the study of the effects of a drug when ingested in extremely high doses is rarely possible before drug marketing. Again, this must await postmarketing pharmacoepidemiology studies.

Finally, it is only in the past decade or two that our society has become more sensitive to the costs of medical care, and the techniques of health economics have been applied to evaluate the cost implications of drug use. It is clear that the exploration of the costs of drug use requires consideration of more than just the costs of the drugs themselves. The costs of a drug's adverse effects may be substantially higher than the cost of the drug itself if these adverse effects result in additional medical care and possibly even hospitalizations. Conversely, a drug's beneficial effects could reduce the need for medical care, resulting in savings that can be much

larger than the cost of the drug itself. As with studies of drug utilization, the economic implications of drug use can be predicted prior to marketing, but can only be rigorously studied after marketing (see Chapter 22).

GENERAL CONTRIBUTIONS OF PHARMACOEPIDEMOLOGY

Lastly, it is important to review the general contributions that can be made by pharmacoepidemiology. As an academic or a clinician, one is most interested in the new information about drug effects and drug costs that can be gained from pharmacoepidemiology. Certainly, these are the findings that receive the greatest public and political attention. However, often no new information is obtained, particularly about new adverse drug effects. This is not a disappointing outcome, but in fact a very reassuring one, and this reassurance about drug safety is one of the most important contributions that can be made by pharmacoepidemiology studies. Related to this is the reassurance that the sponsor of the study, whether manufacturer or regulator, is fulfilling its organizational duty ethically and responsibly by looking for any undiscovered problems which may be there. In an era of product liability litigation, this is an important assurance. One cannot change whether a drug causes an adverse reaction, and the fact that it does will hopefully eventually become evident. What can be changed is the perception about whether a manufacturer did everything possible to detect it and, so, whether it was negligent in its behavior.

Key Points

- *Pharmacoepidemiology* is the study of the use of and the effects of drugs in large numbers of people. It uses the methods of epidemiology to study the content area of clinical pharmacology.
- The history of pharmacoepidemiology is a history of increasingly frequent accusations about adverse drug reactions, often arising out of the spontaneous reporting system, followed by formal studies proving or disproving those associations.
- The drug approval process is inherently limited, so it cannot detect, before marketing, adverse effects that are uncommon, delayed, unique to high risk populations, due to misuse of the drugs by prescribers or patients, etc.
- Pharmacoepidemiology can contribute information about drug safety and effectiveness that is not available from premarketing studies.

SUGGESTED FURTHER READINGS

- Califf RM. The need for a national infrastructure to improve the rational use of therapeutics. *Pharmacoepidemiol Drug Saf* 2002; **11**: 319–27.
- Caranasos GJ, Stewart RB, Cluff LE. Drug-induced illness leading to hospitalization. *JAMA* 1974; **228**: 713–17.
- Cluff LE, Thornton GF, Seidl LG. Studies on the epidemiology of adverse drug reactions. I. Methods of surveillance. *JAMA* 1964; **188**: 976–83.
- Crane J, Pearce N, Flatt A, Burgess C, Jackson R, Kwong T, *et al*. Prescribed fenoterol and death from asthma in New Zealand, 1981–83: case-control study. *Lancet* 1989; **1**: 917–22.
- Erslev AJ, Wintrobe MM. Detection and prevention of drug induced blood dyscrasias. *JAMA* 1962; **181**: 114–19.
- Geiling EMK, Cannon PR. Pathogenic effects of elixir of sulfanilimide (diethylene glycol) poisoning. *JAMA* 1938; **111**: 919–26.
- Guidelines For Good Pharmacoepidemiology Practices. *Pharmacoepidemiol Drug Saf* 2005; **14**: 589–95.
- Herbst AL, Ulfelder H, Poskanzer DC. Adenocarcinoma of the vagina: association of maternal stilbestrol therapy with tumor appearance in young women. *N Engl J Med* 1971; **284**: 878–81.
- Joint Commission on Prescription Drug Use. *Final Report*. Washington, DC, 1980.
- Kimmel SE, Keane MG, Crary JL, Jones J, Kinman JL, Beare J, *et al*. Detailed examination of fenfluramine-phentermine users with valve abnormalities identified in Fargo, North Dakota. *Am J Cardiol* 1999; **84**: 304–8.
- Kono R. Trends and lessons of SMON research. In: Soda T, ed., *Drug-Induced Sufferings*. Princeton, NJ: Excerpta Medica, 1980; p. 11.
- Lazarou J, Pomeranz BH, Corey PN. Incidence of adverse drug reactions in hospitalized patients: a meta-analysis of prospective studies. *JAMA* 1998; **279**: 1200–5.
- Lenz W. Malformations caused by drugs in pregnancy. *Am J Dis Child* 1966; **112**: 99–106.
- Meyler L. *Side Effects of Drugs*. Amsterdam: Elsevier, 1952.
- Miller RR, Greenblatt DJ. *Drug Effects in Hospitalized Patients*. New York: John Wiley & Sons, 1976.
- Rawlins MD, Thompson JW. Pathogenesis of adverse drug reactions. In: Davies DM, ed., *Textbook of Adverse Drug Reactions*. Oxford: Oxford University Press, 1977; p. 44.
- Strom BL, Members of the ASCPT Pharmacoepidemiology Section. Position paper on the use of purported postmarketing drug surveillance studies for promotional purposes. *Clin Pharmacol Ther* 1990; **48**: 598.
- Strom BL, Berlin JA, Kinman JL, Spitz PW, Hennessy S, Feldman H, *et al*. Parenteral ketorolac and risk of gastrointestinal and operative site bleeding: a postmarketing surveillance study. *JAMA* 1996; **275**: 376–82.
- Wallerstein RO, Condit PK, Kasper CK, Brown JW, Morrison FR. Statewide study of chloramphenicol therapy and fatal aplastic anemia. *JAMA* 1969; **208**: 2045–50.
- Wright P. Untoward effects associated with practolol administration. Oculomucocutaneous syndrome. *BMJ* 1975; **1**: 595–8.

