Pharmacoepidemiology

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Preface

“. . . If the whole materia medica, as now used, could be sunk to the bottom of the sea, it would be all the better for mankind, and all the worse for the fishes.”

Oliver Wendell Holmes, 
Medical Essays, Comments and Counter-Currents in Medical Science

The history of drug regulation in the United States is largely a history of political responses to epidemics of adverse drug reactions, each adverse reaction of sufficient public health importance to lead to political pressure for regulatory change.

The initial law, the Pure Food and Drug Act, was passed in 1906. It was a response to the excessive adulteration and misbranding of foods and drugs. The 1938 Food, Drug, and Cosmetic Act was passed in reaction to an epidemic of renal failure resulting from a brand of elixir of sulfanilamide formulated with diethylene glycol. The 1962 Kefauver–Harris Amendment to the Food, Drug, and Cosmetic Act was enacted in response to the infamous “thalidomide disaster,” in which children exposed to thalidomide in utero were born with phocomelia, that is with flippers instead of limbs. The resulting regulatory changes led, in part, to the accelerated development of the field of clinical pharmacology, which is the study of the effects of drugs in humans.

Subsequent decades continued to see an accelerating series of accusations about major adverse events possibly associated with drugs. Those discussed in the first edition of this book included liver disease caused by benoxaprofen, subacute myelo-optic-neuropathy (SMON) caused by cloquinal, the oculomucocutaneous syndrome caused by practolol, acute flank pain and renal failure caused by suprofen, liver disease caused by ticrynafen, and anaphylactoid reactions caused by zomepirac. Added in the second edition were cardiac arrhythmias from astemizole and terfenadine; hypertension, seizures, and strokes from postpartum use of bromocriptine; deaths from fenoterol; suicidal ideation from fluoxetine; hypoglycemia from human insulin; birth defects from isotretinoin; cancer from depot medroxyprogesterone; multiple illnesses from silicone breast implants; memory and other central nervous system disturbances from triazolam; and hemolytic anemia and other adverse reactions from temafloxacin. Further added in the third edition were liver toxicity from the combination of amoxicillin and clavulanic acid; liver toxicity from bromfenac; cancer and myocardial infarction from calcium channel blockers; cardiac arrhythmias with cispapride; primary pulmonary hypertension and cardiac valvular disease from dexamfetamine 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; eosinophilia myalgia from tryptophan; anaphylactic reactions from vitamin K; and liver toxicity from troglitazon. Added in the fourth edition were ischemic colitis from alosertan; myocardial infarction from celecoxib, naproxen, and rofecoxib; rhabdomyolysis from cerivastatin; cardiac arrhythmias from grepafloxxacin; stroke from phenylpropanolamine; bronchospasm from ramipril; and many others. New in this fifth edition are progressive multifocal leukoencephalopathy from natalizumab; hepatotoxicity from pemoline and from lumiracoxib; serious cardiovascular complications from rosiglitazon, tegaserod, sibutramine, rimonabant, valdecoxib, pergolide, and propoxyphene; fatal adverse reactions when used with alcohol.
from hydromorphone; and serious and sometimes fatal brain infections from efalizumab. Many of these resulted in drug withdrawals. Published data also suggest that adverse drug reactions could be as much as the fourth leading cause of death. These and other serious but uncommon drug effects have led to the development of new methods to study drug effects in large populations. Academic investigators, the pharmaceutical industry, regulatory agencies, and the legal profession have turned for these methods to the field of epidemiology, the study of the distribution and determinants of disease in populations.

As this edition goes to press, major new changes have been made in drug regulation and organization, largely in response to a series of accusations about myocardial infarction and stroke caused by analgesics, each detected in long-term prevention trials rather than in normal use of the drugs. For example, the pharmacoepidemiology group at the US Food and Drug Administration (FDA) is being doubled in size, FDA has been given new regulatory authority after drug marketing, and has also been charged with developing the Sentinel Initiative, a program to conduct medical product safety surveillance in a population to exceed 100 million. Further, the development since January 1, 2006 of Medicare Part D, a US federal program to subsidize prescription drugs for Medicare recipients, introduces to pharmacoepidemiology a new database with a stable population of 25 million, as well as the interest of what may be the largest health-care system in the world. These developments portend major changes for our field.

The joining of the fields of clinical pharmacology and epidemiology resulted in the development of a new field: pharmacoepidemiology, the study of the use of and the effects of drugs in large numbers of people. Pharmacoepidemiology applies the methods of epidemiology to the content area of clinical pharmacology. This new field became the science underlying postmarketing drug surveillance, studies of drug effects that are performed after a drug has been released to the market. In recent years, pharmacoepidemiology has expanded to include many other types of studies, as well.

The field of pharmacoepidemiology has grown enormously since the publication of the first edition of this book. The International Society of Pharmacoepidemiology (ISPE), an early idea when the first edition of this book was written, has grown into a major international scientific force, with over 1280 members from 52 countries, an extremely successful annual meeting attracting close to 1000 attendees, a large number of very active committees and scientific interest groups, and its own journal (Pharmacoepidemiology and Drug Safety). In addition, a number of established journals have targeted pharmacoepidemiology manuscripts as desirable. As new scientific developments occur within mainstream epidemiology, they are rapidly adopted, applied, and advanced within our field as well. We have also become institutionalized as a subfield within the field of clinical pharmacology, with a Pharmacoepidemiology Section within the American Society for Clinical Pharmacology and Therapeutics, recently reorganized into a Section on Drug Safety, and with pharmacoepidemiology a required part of the clinical pharmacology board examination.

Most of the major international pharmaceutical companies have founded dedicated units to organize and lead their efforts in pharmacoepidemiology, pharmacoconomics, and quality-of-life studies. The continuing parade of drug safety crises continues to emphasize the need for the field, and some foresighted manufacturers have begun to perform “prophylactic” pharmacoepidemiology studies, to have data in hand and available when questions arise, rather than waiting to begin to collect data after a crisis has developed. Pharmacoepidemiologic data are now routinely used for regulatory decisions, and many governmental agencies have been developing and expanding their own pharmacoepidemiology programs. Risk management programs are now required by regulatory bodies with the marketing of new drugs, as a means of improving drugs’ benefit–risk balance, and manufacturers are scrambling to respond. Requirements that a drug be proven to be cost-effective have been added to national, local, and insurance health-care systems, either to justify reimbursement or even to justify drug availability. A number of schools of medicine,
pharmacy, and public health have established research programs in pharmacoepidemiology, and a few of them have also established pharmacoepidemiology training programs in response to a desperate need for more pharmacoepidemiology manpower. Pharmacoepidemiologic research funding is now more plentiful, and even limited support for training is now available.

In the United States, drug utilization review programs are required, by law, of each of the 50 state Medicaid programs, and have been implemented as well in many managed care organizations. Now, years later however, the utility of drug utilization review programs is being questioned. In addition, the Joint Commission on Accreditation of Health Care Organizations now requires that every hospital in the country have an adverse drug reaction monitoring program and a drug use evaluation program, turning every hospital into a mini-pharmacoepidemiology laboratory. Stimulated in part by the interests of the World Health Organization and the Rockefeller Foundation, there is even substantial interest in pharmacoepidemiology in the developing world. Yet, throughout the world, the increased concern by the public about privacy has made pharmacoepidemiologic research much more difficult.

In the first edition, the goal was to help introduce this new field to the scientific world. The explosion in interest in the field, the rapid scientific progress that has been made, and the unexpected sales of the first edition led to the second edition. The continued maturation of what used to be a new field, the marked increase in sales of the second edition over the first, and the many requests from people all over the world, led to the third edition. Thereafter, much in the field has changed, and the fourth edition was prepared. We also prepared a textbook version, which has been widely used. Now, six years after the fourth edition, the field continues to rapidly change, so it is time for a new edition. For this edition as well, we now include two co-editors who have both shared the work and contributed many important new ideas.

In the process, most chapters in the new edition have been thoroughly revised. Ten new chapters have been added, along with many new authors. With some reorganization of some sections and careful pruning of old chapters, the net size has been kept the same.

As in earlier editions, Part I of this book provides background information on what is included in the field of pharmacoepidemiology, a description of the study designs it uses, a description of its unique problem—the requirement for very large sample sizes—and a discussion about when one would want to perform a pharmacoepidemiology study. Also included is a chapter providing basic principles of clinical pharmacology. Part II presents a series of discussions on the need for the field, the contributions it can make, and some of its problems, from the perspectives of academia, industry, regulatory agencies, and the law. Part III describes the systems that have been developed to perform pharmacoepidemiologic studies, and how each approaches the problem of gathering large sample sizes of study subjects in a cost-effective manner. We no longer attempt to include all the databases in the field, as they have continued to multiply. Instead, in this edition we have combined databases into categories, rather than dedicating a separate chapter to each database. Part IV describes selected special opportunities for the application of pharmacoepidemiology to address major issues of importance. These are of particular interest as the field continues to turn its attention to questions beyond just those of adverse drug reactions. Part V presents state-of-the-art discussions of some particular methodologic issues that have arisen in the field. Finally, Part VI provides our personal speculations about the future of the field. Our expectation is that Parts I, II, III, and VI of this book will be of greatest interest to those new to the field. In contrast, Parts III, IV, V, and VI should be of greatest interest to those with some background, who want a more in-depth view of the field.

This book is not intended as a textbook of adverse drug reactions, that is a compilation of drug-induced problems organized either by drug or by problem. Nor is it intended primarily as a textbook for use in introductory pharmacoepidemiology courses (for which Textbook of Pharmacoepidemiology may be more appropriate).
Rather, it is intended to elucidate the methods of investigating adverse drug reactions, as well as other questions of drug effects. It is also not intended as a textbook of clinical pharmacology, organized by disease or by drug, or a textbook of epidemiology, but rather a text describing the overlap between the two fields.

It is our hope that this book can serve both as a useful introduction to pharmacoepidemiology and a reference source for the growing number of people interested in this field, in academia, in regulatory agencies, in industry, and in the law. It will also hopefully be useful as a reference text for the numerous courses now underway in this field. We have been excited by the rapid progress and growth that our field has seen, and delighted that this book has played a small role in assisting this. With this new edition, it will document the major changes the field has seen. In the process, we hope is that it can continue to serve to assist the field in its development.

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Stephen E. Kimmel
Sean Hennessy

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PART I

Introduction
CHAPTER 1
What is Pharmacoepidemiology?

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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. A 1998 study estimated that 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 pharmacoepidemiology

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 new 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.

Pharmacoepidemiology 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 2).
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 his 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 when used in clinical practice, 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 novel 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 that are the result of an exaggerated but otherwise usual pharmacologic effect of the drug, sometimes called Type A reactions, versus those that 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 (see also Chapter 34). Third, they may have normal drug levels, but for some reason are overly sensitive to them (see Chapter 34).

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; see Chapter 34) or due to some other mechanism. Regardless, Type B reactions are the most difficult to predict or even detect, and represent the major focus of many pharmacoepidemiologic studies of adverse drug reactions.

One typical approach to studying adverse drug reactions has been the collection of spontaneous reports of drug-related morbidity or mortality (see Chapter 10), sometimes called pharmacovigilance (although at other times this term is used to refer to all of pharmacoepidemiology). However, determining causation in case reports of adverse reactions can be problematic (see Chapter 33), as can attempts to compare the effects of drugs in the same class (see Chapter 32). This has led academic investigators, industry, FDA, and the legal com-
Chapter 1: What is Pharmacoepidemiology?

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

Early legislation
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 sulfanilamide dissolved in diethylene glycol. In response, Congress passed the 1938 Food, Drug, and Cosmetic Act. 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

munity to turn to the field of epidemiology. Specifically, studies of adverse effects have been supplemented with studies of adverse events (ADEs). 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 field: pharmacoepidemiology.

Pharmacoepidemiology versus epidemiology
Epidemiology is the study of the distribution and determinants of diseases in populations (see Chapter 3). 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, that is, epidemics. It has since been expanded to encompass 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, 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. Now, as will be made clearer in future chapters, pharmacoepidemiology is considered of importance in the whole life cycle of a drug, from the time when it is first discovered or synthesized through when it is no longer sold as a drug.
Part I: Introduction

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. 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 DESI (Drug Efficacy Study Implementation) process, conducted by the National Academy of Sciences’ National Research Council with support from a contract from FDA, was not completed until years later, 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.

Drug crises and resulting regulatory actions

Despite the more stringent process for drug regulation, subsequent years have seen a series of major adverse drug reactions. Subacute myelo-optic neuropathy (SMON) was found in Japan to be caused by clioquinol, a drug marketed in the early 1930s but not discovered to cause this severe neurological reaction until 1970. 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 10).

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 pharmacologic and toxicologic testing before a drug could be tested in man. The data from these studies were required to be submitted to the FDA in an Investigational New Drug (IND) Application 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 DESI (Drug Efficacy Study Implementation) process, conducted by the National Academy of Sciences’ National Research Council with support from a contract from FDA, was not completed until years later, 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.