# Pharmacoepidemiology

SIXTH EDITION

EDITED BY

Brian L. Strom
Stephen E. Kimmel
Sean Hennessy

WILEY Blackwell

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Sixth Edition

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*Edition History*
5e 2012 John Wiley & Sons Ltd.



*Registered Offices*
John Wiley & Sons, Inc., 111 River Street, Hoboken, NJ 07030, USA
John Wiley & Sons Ltd, The Atrium, Southern Gate, Chichester, West Sussex, PO19 8SQ, UK

*Editorial Office*
9600 Garsington Road, Oxford, OX4 2DQ, UK

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*Library of Congress Cataloging-in-Publication Data*
Names: Strom, Brian L., editor. | Kimmel, Stephen E., editor. | Hennessy, Sean, editor.
Title: Pharmacoepidemiology / edited by Brian L. Strom, Stephen E. Kimmel, Sean Hennessy.
Other titles: Pharmacoepidemiology (Strom)
Description: Sixth edition. | Hoboken, NJ : Wiley-Blackwell, 2020. | Includes bibliographical references and index.
Identifiers: LCCN 2019029935 (print) | ISBN 9781119413417 (cloth) | ISBN 9781119413370 (adobe pdf) | ISBN 9781119413424 (epub)
Subjects: MESH: Pharmacoepidemiology–methods
Classification: LCC RM301.5 (print) | LCC RM301.5 (ebook) | NLM QV 771 | DDC 615.7–dc23 LC record available at https://lccn.loc.gov/2019029935
LC ebook record available at https://lccn.loc.gov/2019029936

Cover images: © jokerpro/iStock.com, © crisserbug/iStock.com, © AlexRaths/iStock.com
Cover design by Wiley

Set in 10/12pt Warnock by SPi Global, Pondicherry, India

10 9 8 7 6 5 4 3 2 1

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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
> *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 clioquinol, 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 amoxicillin-clavulanic acid; liver toxicity from bromfenac; cancer and myocardial infarction from calcium channel blockers; cardiac arrhythmias with cisapride; 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; eosinophilia myalgia from tryptophan; anaphylactic

reactions from vitamin K; and liver toxicity from troglitazone. Added in the fourth edition were ischemic colitis from alosetron; myocardial infarction from celecoxib, naproxen, and rofecoxib; rhabdomyolysis from cerivastatin; cardiac arrhythmias from grepafloxacin; stroke from phenylpropanolamine; bronchospasm from rapacuronium; and many others. Added in the fifth edition were progressive multifocal leukoencephalopathy from natalizumab; hepatotoxicity from pamoline and from lumiracoxib; serious cardiovascular complications from rosiglitazone, tegaserod, sibutramine, rimonabant, valdecoxib, pergolide, and propoxyphene; fatal adverse reactions when used with alcohol from palladone; and serious and sometimes fatal brain infections from efalizumab. New in the sixth edition are serious infections of the genital area from sodium-glucose Cotransporter-2 (SGLT2) inhibitors; serious low blood sugar levels and mental health side effects from fluoroquinolones; increased risk of heart-related death and death from all causes from gout medicine febuxostat; increased risk of leg and foot amputations from canagliflozin; possible increased risk of bladder cancer from pioglitazone; heart failure risk from saxagliptin and alogliptin; possible increased risk of heart attack and stroke from testosterone; and potentially fatal heart rhythms from azithromycin. Some 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.

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) was doubled in size; the FDA was given new regulatory authority after drug marketing, and was also 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 healthcare system in the world. These developments have brought about major changes for our field.

The bridging of the fields of clinical pharmacology and epidemiology resulted in the development of a new field: pharmacoepidemiology, the study of the use of and 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, an early idea when the first edition was written, has grown into a major international scientific force, with over 1476 members from 63 countries, an extremely successful annual meeting attracting more than 1800 attendees, a large number of very active committees and special interest groups, and its own journal. 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 too. We have also become institutionalized as a subfield within the field of clinical pharmacology, with a Drug Utilization and Outcomes community within the American Society for Clinical Pharmacology and Therapeutics, 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, pharmacoeconomics, 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, so as to have data in hand and available when questions arise, rather than waiting to begin collecting 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. Requirements that a drug be proven to be cost-effective have been added to national, local, and insurance healthcare 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 a bigger pharmacoepidemiology labor force. Pharmacoepidemiologic research funding is now more plentiful, and even support for training is now available, albeit limited.

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. However now, years later, the utility of drug utilization review programs has been questioned. In addition, the Joint Commission currently requires that every hospital in the US has 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 public's increased concern about privacy has made pharmacoepidemiologic research much more difficult.

In the first edition of this book, the goal was to help introduce this new field to the scientific world. The explosion in interest in the area, the rapid scientific progress that has been made, and the unexpectedly good sales of the first edition led to the second. The continued maturation of what used to be a novel 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 produced a textbook version, which has been widely used. Now, seven years after the fifth edition, the field continues to rapidly change, so it is time for a new edition.

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

As in earlier editions, Part I provides background information on what is included in the field of pharmacoepidemiology, a description of the study designs it uses, a consideration 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, and regulatory agencies. 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. 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 pharmacoepidemiology.

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* might 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 as 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 as 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 subject. 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 that have occurred. In the process, we hope that it can continue to serve to assist in the development of pharmacoepidemiology.

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## Acknowledgments

There are many individuals and institutions to whom we owe thanks for their contributions to our efforts in preparing this book. Mostly, we thank the contributors who wrote the chapters within it. We greatly enjoyed interacting with them and are grateful for all that we have learned in the process. Over the years, our own pharmacoepidemiology work has been supported mostly by grants, contracts, and cooperative agreements from the US government, especially multiple different institutes of the National Institutes of Health, the Agency for Healthcare Research and Quality, the Food and Drug Administration, and the Department of Veterans Affairs, as well as the Patient Centered Outcomes Research Institute. Other significant funders of our work include private foundations and pharmaceutical companies. Also, we would like to thank the University of Pennsylvania Perelman School of Medicine and Rutgers University. While none of this funding was specifically intended to support the development of this book, without the assistance we would not have been able to develop our careers in pharmacoepidemiology. In addition, we would like to thank Wiley, our publisher, for assistance and insights, both in support of this book and in support of the field's journal, *Pharmacoepidemiology and Drug Safety*.

Chris Rowan's contributions to this book were enormous, encompassing both the role of Managing Editor and reviewing all of the chapters, editing them thoughtfully, and posing additional questions and issues for the authors to address. Finally, Jennifer Hardy provided superb help communicating with the authors and preparing the chapters for submission to Wiley.

BLS would like to thank Steve Kimmel and Sean Hennessy for joining him as co-editors in this and the prior edition. They are two very special and talented men. It has been BLS's pleasure to help to train them, now too many years ago, to help them cultivate their own careers, and to see them blossom into star pharmacoepidemiologists in their own right, now extremely effective and successful. It is a wonderful to be able to share with them this book, which has been an important part of BLS's life and career.

BLS would also like to thank his late parents for the support and education that were critical to his being able to be successful in his career. He would like to thank the late Paul D. Stolley, MD, MPH, and the late Kenneth L. Melmon, MD, for their direction, guidance, and inspiration in the formative years of his career. He would like to thank his trainees, from whom he learns at least as much as he teaches. Last, but certainly not least, BLS would like to thank his family – Lani, Shayna, and Jordi – for accepting the time demands of the book, for tolerating his endless hours working at home on it, and for their ever-present love and support.

SEK expresses his sincere gratitude to BLS for his almost 30 years as a mentor and colleague and for the chance to work on this book, to his parents for providing the foundation for all of his work, and to his family – Alison, David, Benjamin, and Jonathan – for all their support and patience while Dad worked on the book.

SH also thanks BLS, his longtime friend and career mentor, and all of his students, mentees, and collaborators. Finally, he thanks his parents, and his family – Kristin, Landis, and Bridget – for their love and support.

# Part I

# Introduction

# 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 it had before. Although this has given healthcare providers the ability to provide better medical care for their patients, it has resulted too 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, and 1.5 million US hospitalizations each year result from adverse drug reactions; yet, 20–70% of adverse drug reactions may be preventable [1]. 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 in addition many issues other than adverse reactions.

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 outlined, 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

*Pharmacoepidemiology*, Sixth Edition. Edited by Brian L. Strom, Stephen E. Kimmel and Sean Hennessy.

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 particular patient at hand. This individualization of therapy requires the determination of a risk/benefit ratio specific to the patient. 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 [2]. 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 who is 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 which are the result of an exaggerated but otherwise usual pharmacologic effect of the drug, sometimes called *type A reactions*, versus those which are aberrant effects, so called *type B reactions* [3]. 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 it unusually slowly, leading to drug levels that are too high (see also Chapter 2). Third, they may have normal drug levels, but for some reason are overly sensitive to the drug.

In contrast, type B reactions tend to be uncommon, not related to dose, unpredictable,