Pharmacoepidemiology
Pharmacoepidemiology

Sixth Edition

Edited by

Brian L. Strom MD, MPH
Chancellor, Rutgers Biomedical & Health Sciences
Executive Vice President for Health Affairs
University Professor
Rutgers, the State University of New Jersey
Newark, NJ, USA

Stephen E. Kimmel MD, MSCE
Professor of Medicine and of Epidemiology
Senior Scholar, Center for Clinical Epidemiology and Biostatistics
University of Pennsylvania Perelman School of Medicine
Philadelphia, PA, USA

Sean Hennessy PharmD, PhD
Professor of Epidemiology
Senior Scholar, Center for Clinical Epidemiology and Biostatistics
University of Pennsylvania Perelman School of Medicine
Philadelphia, PA, USA
Contents

Contributors x
Preface xix
Acknowledgments xxiii

Part I Introduction 1

1 What Is Pharmacoepidemiology? 3
   Brian L. Strom

2 Basic Principles of Clinical Pharmacology Relevant to Pharmacoepidemiologic Studies 27
   Jeffrey S. Barrett

3 Basic Principles of Clinical Epidemiology Relevant to Pharmacoepidemiologic Studies 44
   Brian L. Strom

4 Sample Size Considerations for Pharmacoepidemiologic Studies 60
   Brian L. Strom

5 When Should One Perform Pharmacoepidemiologic Studies? 71
   Brian L. Strom

Part II The Role of Pharmacoepidemiology in Different Sectors 81

6 The Role of Pharmacoepidemiology in the Healthcare System and Academia 83
   Joshua J. Gagne and Jerry Avorn

7 The Role of Pharmacoepidemiology in Industry 98
   Nicole M. Gatto, Rachel E. Sobel, Jamie Geier, Jingping Mo, Andrew Bate, and Robert F. Reynolds
8 The Role of Pharmacoepidemiology in Regulatory Agencies  126
Gerald J. Dal Pan, June Raine, and Shinobu Uzu

9 Pharmacoepidemiology and the Law  140
Aaron S. Kesselheim and Kerstin N. Vokinger

Part III Sources of Data for Pharmacoepidemiology Research  165

Part IIIa Spontaneous Reporting  167

10 Postmarketing Spontaneous Pharmacovigilance Reporting Systems  169
Gerald J. Dal Pan, Marie Lindquist, and Kate Gelperin

Part IIIb Electronic Data Systems  203

11 Overview of Electronic Databases in Pharmacoepidemiology  205
Brian L. Strom

12 Encounter Databases  211
Tobias Gerhard, Yola Moride, Anton Pottegård, and Nicole Pratt

13 Electronic Health Record Databases  241
Daniel B. Horton, Harshvinder Bhusar, Lucy Carty, Francesca Cunningham, Alexis Ogdie, Janet Sultana, and Gianluca Trifirò

14 Inpatient Databases  290
James A. Feinstein, Peter K. Lindenauer, Chris Feudtner, and Brian T. Fisher

Part IIIc Studies Involving Ad Hoc Data Collection  305

15 Event Monitoring in the UK  307
Vicki Osborne and Saad A.W. Shakir

16 Primary Data Collection for Pharmacoepidemiology  342
Nancy A. Dreyer, Ana Filipa Macedo, and Priscilla Velentgas

Part IIId Choosing a Data Source  355

17 Choosing among the Available Data Sources for Pharmacoepidemiology Research  357
Brian L. Strom
Part IV  Selected Applications of Pharmacoepidemiology  373

18  Studies of Drug Utilization  375
    Björn Wettermark, Vera Vlahović-Palčevski, David Lee, and Ulf Bergman

19  Evaluating and Improving Physician Prescribing  411
    Christine Y. Lu, the late Sumit R. Majumdar, Helene Lipton, and Stephen B. Soumerai

20  Pharmacoepidemiologic Studies of Vaccine Safety  437
    Robert T. Chen, Jason M. Glanz, and Tom T. Shimabukuro

21  Epidemiologic Studies of Medical Devices: Methodologic Considerations for Implantable Devices  496
    Danica Marinac-Dabic, Sharon-Lise Normand, Art Sedrakyan, and Thomas P. Gross

22  Research on the Effects of Medications in Pregnancy and in Children  524
    Daniel B. Horton, Sonia Hernandez-Diaz, Tamar Lasky, and Krista F. Huybrechts

23  Study of Biologics and Biosimilars  561
    Jeffrey R. Curtis and James D. Lewis

24  Risk Management  581
    Claudia Manzo, Emil Cochino, Lubna Merchant, and Giampiero Mazzaglia

25  Distributed Networks of Databases Analyzed Using Common Protocols and/or Common Data Models  617
    Sengwee Toh, Nicole Pratt, Olaf Klungel, Joshua J. Gagne, and Robert W. Platt

26  Comparative Effectiveness Research  639
    Soko Setoguchi and Ian Chi Kei Wong

27  Data Mining and Other Informatics Approaches to Pharmacoepidemiology  675
    Andrew Bate, Gianluca Trifirò, Paul Avillach, and Stephen J.W. Evans

28  Pharmacoepidemiologic Research on Drugs of Abuse  701
    Jana McAninch, Alex Secora, Cynthia Kornegay, and Judy Staffa

Part V  Selected Special Methodologic Issues in Pharmacoepidemiology  723

29  Assessing Causation from Case Reports  725
    Judith K. Jones, Bernard Bégaud, and Elyse Kingery

30  Molecular Pharmacoepidemiology  746
    Christine Y. Lu and Stephen E. Kimmel
<table>
<thead>
<tr>
<th>Chapter</th>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>31</td>
<td>Bioethical Issues in Pharmacoepidemiologic Research</td>
<td>772</td>
</tr>
<tr>
<td></td>
<td>Laura E. Bothwell, Annika Richterich, and Jeremy Greene</td>
<td></td>
</tr>
<tr>
<td>32</td>
<td>The Use of Randomized Controlled Trials in Pharmacoepidemiology</td>
<td>792</td>
</tr>
<tr>
<td></td>
<td>Robert F. Reynolds, Samuel M. Lesko, Nicolle M. Gatto, Tjeerd P. van Staa, and Allen A. Mitchell</td>
<td></td>
</tr>
<tr>
<td>33</td>
<td>The Use of Pharmacoepidemiology to Study Beneficial Drug Effects</td>
<td>813</td>
</tr>
<tr>
<td></td>
<td>Brian L. Strom and the late Kenneth L. Melmon</td>
<td></td>
</tr>
<tr>
<td>34</td>
<td>Pharmacoeconomics: The Economics of Pharmaceuticals</td>
<td>837</td>
</tr>
<tr>
<td></td>
<td>Kevin A. Schulman</td>
<td></td>
</tr>
<tr>
<td>35</td>
<td>Benefit–Risk Assessments of Medical Treatments</td>
<td>867</td>
</tr>
<tr>
<td></td>
<td>Bennett Levitan, Rachael DiSantostefano, and Scott Evans</td>
<td></td>
</tr>
<tr>
<td>36</td>
<td>The Use of Metaanalysis in Pharmacoepidemiology</td>
<td>897</td>
</tr>
<tr>
<td></td>
<td>Jesse A. Berlin, Brenda J. Crowe, H. Amy Xia, and Stephen J.W. Evans</td>
<td></td>
</tr>
<tr>
<td>37</td>
<td>Validity of Drug and Diagnosis Data in Pharmacoepidemiology</td>
<td>948</td>
</tr>
<tr>
<td></td>
<td>Mary Elizabeth Ritchey, Suzanne L. West, and George Maldonado</td>
<td></td>
</tr>
<tr>
<td>38</td>
<td>Studies of Medication Adherence</td>
<td>991</td>
</tr>
<tr>
<td></td>
<td>Julie Lauffenburger, Trisha Acri, and Robert Gross</td>
<td></td>
</tr>
<tr>
<td>39</td>
<td>Risk Evaluation and Communication</td>
<td>1010</td>
</tr>
<tr>
<td></td>
<td>Susan J. Blalock, Rebecca Dickinson, and Peter Knapp</td>
<td></td>
</tr>
<tr>
<td>40</td>
<td>Methods for Studying the Health Effects of Drug–Drug Interactions</td>
<td>1030</td>
</tr>
<tr>
<td></td>
<td>Sean Hennessy, Charles E. Leonard, Joshua J. Gagne, James H. Flory, Colleen M. Brensinger, and Warren B. Bilker</td>
<td></td>
</tr>
<tr>
<td>41</td>
<td>The Pharmacoepidemiology of Medication Errors</td>
<td>1046</td>
</tr>
<tr>
<td></td>
<td>Hanna M. Seidling and David W. Bates</td>
<td></td>
</tr>
<tr>
<td>42</td>
<td>Patient Engagement and Patient-Reported Outcomes</td>
<td>1061</td>
</tr>
<tr>
<td></td>
<td>Esi M. Morgan</td>
<td></td>
</tr>
<tr>
<td>43</td>
<td>Advanced Approaches to Controlling Confounding in Pharmacoepidemiologic Studies</td>
<td>1078</td>
</tr>
<tr>
<td></td>
<td>Sebastian Schneeweiss and Samy Suissa</td>
<td></td>
</tr>
</tbody>
</table>
Contributors

Trisha Acri
Philadelphia, PA
USA

Paul Avillach
Department of Biomedical Informatics
Harvard Medical School
Boston, MA
USA

Jerry Avorn
Division of Pharmacoepidemiology and Pharmacoeconomics
Department of Medicine
Brigham and Women’s Hospital and Harvard Medical School
Boston, MA
USA

Jeffrey S. Barrett
Bill and Melinda Gates Medical Research Institute
Cambridge, MA
USA

Andrew Bate
Pfizer Ltd
Walton-on-the-Hill, Surrey
UK

David W. Bates
Division of General Internal Medicine and Primary Care
Brigham and Women’s Hospital and Harvard Medical School
Boston, MA
USA

Bernard Bégaud
School of Medicine
University of Bordeaux
Bordeaux
France

Ulf Bergman
Division of Clinical Pharmacology
Department of Laboratory Medicine
Centre for Pharmacoepidemiology
Karolinska Institute
Karolinska University Hospital-Huddinge
Stockholm
Sweden

Jesse A. Berlin
Johnson & Johnson
Titusville, NJ
USA

Harshvinder Bhullar
Real-World Insights, IQVIA
London
UK
Warren B. Bilker
University of Pennsylvania Perelman School of Medicine
Philadelphia, PA
USA

Susan J. Blalock
Division of Pharmaceutical Outcomes and Policy
Eshelman School of Pharmacy
University of North Carolina at Chapel Hill
Chapel Hill, NC
USA

Laura E. Bothwell
Health Sciences Department
Worcester State University
Worcester, MA
USA

Colleen M. Brensinger
University of Pennsylvania Perelman School of Medicine
Philadelphia, PA
USA

Lucy Carty
Clinical Practice Research Datalink
Medicines and Healthcare Products Regulatory Agency
London
UK

Robert T. Chen
Brighton Collaboration
Task Force for Global Health
Decatur, GA
USA

Emil Cochino
European Medicines Agency
Amsterdam
The Netherlands

Brenda J. Crowe
Eli Lilly and Company
Indianapolis, IN
USA

Francesca Cunningham
Pharmacy Benefits Management, and Center for Medication Safety
US Department of Veterans Affairs
Hines, IL
USA

Jeffrey R. Curtis
Division of Clinical Immunology & Rheumatology
University of Alabama at Birmingham
Birmingham, AL
USA

Gerald J. Dal Pan
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research
US Food and Drug Administration
Silver Spring, MD
USA

Rebecca Dickinson
School of Health and Community Studies
Leeds Beckett University
Leeds
UK

Rachael L. DiSantostefano
Janssen Research & Development
Titusville, NJ
USA

Nancy A. Dreyer
IQVIA Real-World & Analytic Solutions
Boston, MA
USA
Scott Evans  
Biostatistics Center  
The George Washington University  
Rockville, MD  
USA

Stephen J.W. Evans  
Department of Medical Statistics  
London School of Hygiene and Tropical Medicine  
London  
UK

James A. Feinstein  
Adult & Child Health Consortium for Health Outcomes Research and Delivery Science  
University of Colorado School of Medicine  
Aurora, CO  
USA

Chris Feudtner  
Center for Pediatric Clinical Effectiveness and PolicyLab  
The Children's Hospital of Philadelphia  
Philadelphia, PA  
USA

Brian T. Fisher  
Division of Infectious Diseases  
The Children’s Hospital of Philadelphia  
Philadelphia, PA  
USA

James H. Flory  
Memorial Sloan Kettering Cancer Center  
New York, NY  
USA

Joshua J. Gagne  
Division of Pharmacoepidemiology and Pharmacoeconomics  
Department of Medicine  
Brigham and Women's Hospital and Harvard Medical School  
Boston, MA, USA

Nicolle M. Gatto  
Department of Epidemiology, Worldwide Research and Development  
Pfizer, Inc.  
New York, NY  
USA

Jamie Geier  
Department of Epidemiology, Worldwide Research and Development  
Pfizer, Inc.  
New York, NY  
USA

Kate Gelperin  
Division of Epidemiology  
Office of Surveillance and Epidemiology  
Center for Drug Evaluation and Research  
US Food and Drug Administration  
Silver Spring, MD  
USA

Tobias Gerhard  
Rutgers Center for Pharmacoepidemiology and Treatment Science  
Rutgers Ernest Mario School of Pharmacy  
New Brunswick, NJ  
USA

Jason M. Glanz  
Institute for Health Research  
Kaiser Permanente Colorado  
and  
Department of Epidemiology  
Colorado School of Public Health  
Denver, CO  
USA

Jeremy A. Greene  
Department of the History of Medicine  
The Johns Hopkins University School of Medicine  
Baltimore, MD  
USA
Robert Gross
Departments of Medicine (ID) and
Epidemiology/Biostatistics/Informatics
Center for Clinical Epidemiology and Biostatistics
University of Pennsylvania Perelman School
of Medicine
Philadelphia, PA
USA

Thomas P. Gross
Office of Surveillance and Biometrics
Center for Devices and Radiological Health
US Food and Drug Administration
Silver Spring, MD
USA

Sean Hennessy
Center for Clinical Epidemiology and Biostatistics
University of Pennsylvania Perelman School of Medicine
Philadelphia, PA
USA

Sonia Hernandez-Diaz
Department of Epidemiology
Harvard T.H. Chan School of Public Health
Boston, MA
USA

Daniel B. Horton
Department of Pediatrics
Rutgers Robert Wood Johnson Medical School
Rutgers Center for Pharmacoepidemiology and Treatment Science
New Brunswick, NJ
USA

Krista F. Huybrechts
Division of Pharmacoepidemiology and Pharmacoeconomics
Department of Medicine
Brigham and Women’s Hospital and Harvard Medical School
Boston, MA
USA

Judith K. Jones
PharmaLex, Inc.
Fairfax, VA
University of Michigan School of Public Health
Summer Program
Ann Arbor, MI
Georgetown University School of Medicine
Washington, DC
USA

Aaron S. Kesselheim
Program On Regulation, Therapeutics, And Law (PORTAL)
Division of Pharmacoepidemiology and Pharmacoeconomics
Department of Medicine
Brigham and Women’s Hospital and Harvard Medical School
Boston, MA
USA

Stephen E. Kimmel
Center for Clinical Epidemiology and Biostatistics
University of Pennsylvania Perelman School of Medicine
Philadelphia, PA
USA

Elyse Kingery
Degge Group, Ltd., a PharmaLex Company
Fairfax, VA
USA

Olaf Klungel
Division of Pharmacoepidemiology & Clinical Pharmacology
Utrecht Institute for Pharmaceutical Sciences (UIPS)
Utrecht University
Utrecht
The Netherlands
Peter Knapp
Department of Health Sciences and the Hull York Medical School
University of York
York
UK

Cynthia Kornegay
Division of Epidemiology
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research
US Food and Drug Administration
Silver Spring, MD
USA

Tamar Lasky
Office of Biostatistics and Epidemiology
Center for Biologics Evaluation and Research
US Food and Drug Administration
Silver Spring, MD
USA

Julie Lauffenburger
Division of Pharmacoepidemiology and
Pharmacoeconomics and Center for Healthcare Delivery Sciences
Brigham and Women’s Hospital and Harvard Medical School
Boston, MA
USA

David Lee
Pharmaceuticals and Health Technologies Group
Management Sciences for Health
Arlington, VA
USA

Charles E. Leonard
University of Pennsylvania Perelman School of Medicine
Philadelphia, PA
USA

Samuel M. Lesko
Northeast Regional Cancer Institute
Scranton, PA
USA

Bennett Levitan
Department of Epidemiology
Janssen Research & Development
Titusville, NJ
USA

James D. Lewis
Department of Medicine
Division of Gastroenterology
Department of Biostatistics, Epidemiology, and Informatics
Perelman School of Medicine University of Pennsylvania
Philadelphia, PA
USA

Peter K. Lindenauer
Center for Quality of Care Research
Baystate Medical Center
Springfield, MA
USA

Marie Lindquist
Uppsala Monitoring Centre
WHO Collaborating Centre for International Drug Monitoring
Uppsala
Sweden

Helene Lipton
School of Medicine and Pharmacy
University of California at San Francisco
San Francisco, CA
USA

Christine Y. Lu
Department of Population Medicine
Harvard Medical School and Harvard Pilgrim Health Care Institute
Boston, MA
USA
Ana Filipa Macedo
Real-World Evidence Solutions Division
QuintilesIMS
Madrid
Spain

Sumit R. Majumdar (deceased)
Formerly of Department of Medicine
Faculty of Medicine and Dentistry
University of Alberta
Edmonton, Alberta
Canada

George Maldonado
Division of Environmental Health Sciences
School of Public Health
University of Minnesota
Minneapolis, MN
USA

Claudia Manzo
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research
US Food and Drug Administration
Silver Spring, MD
USA

Danica Marinac-Dabic
Office of Clinical Evidence and Analysis
Center for Devices and Radiological Health
US Food and Drug Administration
Silver Spring, MD
USA

Giampiero Mazzaglia
European Medicines Agency
Amsterdam
The Netherlands

Jana McAninch
Division of Epidemiology
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research
US Food and Drug Administration
Silver Spring, MD
USA

Kenneth L. Melmon (deceased)
Formerly of Stanford University School of Medicine
Stanford, CA
USA

Lubna Merchant
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research
US Food and Drug Administration
Silver Spring, MD
USA

Allen A. Mitchell
Slone Epidemiology Center at Boston University
Boston, MA
USA

Jingping Mo
Department of Epidemiology, Worldwide Research and Development
Pfizer, Inc.
New York, NY
USA

Esi M. Morgan
Department of Pediatrics
Division of Rheumatology
Cincinnati Children’s Hospital Medical Center
University of Cincinnati College of Medicine
Cincinnati, OH
USA

Yola Moride
Faculty of Pharmacy
Université de Montréal
Montreal, Quebec
Canada
Rutgers Center for Pharmacoepidemiology and Treatment Science
New Brunswick, NJ
USA
Sharon-Lise Normand  
Department of Health Care Policy  
Harvard Medical School  
and  
Department of Biostatistics  
Harvard T.H. Chan School of Public Health  
Boston, MA  
USA  

Alexis Ogdie  
University of Pennsylvania Perelman School of Medicine  
Philadelphia, PA  
USA  

Vicki Osborne  
Drug Safety Research Unit  
Southampton  
UK  

Robert W. Platt  
Departments of Epidemiology, Biostatistics, and Occupational Health, and of Pediatrics  
McGill University  
Montreal, Quebec  
Canada  

Anton Pottegård  
Clinical Pharmacology and Pharmacy  
Department of Public Health  
University of Southern Denmark  
Odense  
Denmark  

Nicole Pratt  
Quality Use of Medicines and Pharmacy Research Centre  
School of Pharmacy and Medical Sciences  
University of South Australia  
Adelaide, South Australia  
Australia  

June Raine  
Medicines and Healthcare Products Regulatory Agency  
London  
UK  

Robert F. Reynolds  
Department of Epidemiology  
Global Medical Value, Evidence and Outcomes  
GlaxoSmithKline  
Upper Providence, PA  
USA  

Annika Richterich  
Faculty of Arts & Social Sciences  
Maastricht University  
Maastricht  
The Netherlands  

Mary Elizabeth Ritchey  
RTI Health Solutions  
RTI International  
Research Triangle Park, NC  
USA  

Sebastian Schneeweiss  
Harvard Medical School  
Harvard T.H. Chan School of Public Health  
Division of Pharmacoepidemiology  
Department of Medicine  
Brigham and Women's Hospital  
Boston, MA  
USA  

Kevin A. Schulman  
Clinical Excellence Research Center  
Department of Medicine  
Stanford University  
Stanford, CA  
USA
Alex Secora  
Division of Epidemiology  
Office of Surveillance and Epidemiology  
Center for Drug Evaluation and Research  
US Food and Drug Administration  
Silver Spring, MD  
USA

Art Sedrakyan  
Weill Cornell Medical College  
New York, NY  
USA

Hanna M. Seidling  
Division of General Internal Medicine and Primary Care  
Brigham and Women’s Hospital and Harvard Medical School  
Boston, MA  
USA  
Department of Clinical Pharmacology and Pharmacoepidemiology  
Cooperation Unit Clinical Pharmacy  
University Hospital Heidelberg  
Heidelberg  
Germany

Soko Setoguchi  
Rutgers Robert Wood Johnson Medical School  
Rutgers Center for Pharmacoepidemiology and Treatment Science  
New Brunswick, NJ  
USA

Saad A.W. Shakir  
Drug Safety Research Unit  
Southampton  
UK

Tom T. Shimabukuro  
Immunization Safety Office  
Division of Healthcare Quality Promotion Centers for Disease Control and Prevention  
Atlanta, GA  
USA

Rachel E. Sobel  
Department of Epidemiology, Worldwide Research and Development  
Pfizer, Inc.  
New York, NY  
USA

Stephen B. Soumerai  
Department of Population Medicine  
Harvard Medical School and Harvard Pilgrim Health Care Institute  
Boston, MA  
USA

Tjeerd P. van Staa  
Health eResearch Centre  
University of Manchester  
Manchester  
UK

Judy Staffa  
Office of Surveillance and Epidemiology  
Center for Drug Evaluation and Research  
US Food and Drug Administration  
Silver Spring, MD  
USA

Brian L. Strom  
Rutgers Center for Pharmacoepidemiology and Treatment Science  
Rutgers Biomedical and Health Sciences  
Newark, NJ  
USA

Samy Suissa  
McGill University  
Centre for Clinical Epidemiology  
Lady Davis Research Institute – Jewish General Hospital  
Montreal, Quebec  
Canada
Janet Sultana
Department of Biomedical and Dental Sciences and Morphofunctional Imaging
University of Messina
Messina
Italy

Sengwee Toh
Department of Population Medicine
Harvard Medical School and Harvard Pilgrim Health Care Institute
Boston, MA
USA

Gianluca Trifirò
Department of Biomedical and Dental Sciences and Morphofunctional Imaging
University of Messina
Messina
Italy

Shinobu Uzu
Pharmaceuticals and Medical Devices Agency
Tokyo
Japan

Priscilla Velentgas
IQVIA, Real-World Insights
Cambridge, MA
USA

Vera Vlahović-Palčevski
Department of Clinical Pharmacology
University Hospital Rijeka
Department of Pharmacology
University of Rijeka Medical Faculty
Department of Basic Medical Sciences
Faculty of Health Studies
Rijeka
Croatia

Kerstin N. Vokinger
Program On Regulation, Therapeutics, And Law (PORTAL)
Division of Pharmacoepidemiology and Pharmacoeconomics
Department of Medicine
Brigham and Women's Hospital
Harvard Medical School
Boston, MA
USA

Suzanne L. West
RTI International
Research Triangle Park, NC
Department of Epidemiology
Gillings School of Global Public Health
University of North Carolina
Chapel Hill, NC
USA

Björn Wettermark
Division of Clinical Pharmacology
Department of Laboratory Medicine
Centre for Pharmacoepidemiology
Karolinska Institute
Karolinska University Hospital-Huddinge
Stockholm
Sweden

Ian Chi Kei Wong
Department of Pharmacology and Pharmacy
University of Hong Kong
Hong Kong
UCL School of Pharmacy
London
UK

H. Amy Xia
Amgen, Inc.
Thousand Oaks, CA
USA
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, ocular mucocutaneous 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 pamolime and from lumiracoxib; serious cardiovascular complications from rosiglitazone, tegaserod, sibutramine, rimonabant, valdecoxb, 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 maturaation 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.

Brian L. Strom, MD, MPH
Stephen E. Kimmel, MD, MSCE
Sean Hennessy, PharmD, PhD
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
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

What Is Pharmacoepidemiology?

Brian L. Strom

Rutgers Biomedical and Health Sciences, Newark, NJ, USA
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,