



TEXTBOOK OF

# Pharmacoepidemiology

Third Edition

Edited by  
**Brian L. Strom**  
**Stephen E. Kimmel**  
**Sean Hennessy**

WILEY Blackwell



## **Textbook of Pharmacoepidemiology**



# Textbook of Pharmacoepidemiology

Third 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**

*Dean's Professor and Chair of Epidemiology  
College of Public Health and Health Professions and College of Medicine  
University of Florida  
Gainesville, FL, USA*

**Sean Hennessy, PharmD, PhD**

*Professor of Epidemiology  
Director, Center for Pharmacoepidemiology Research and Training  
University of Pennsylvania Perelman School of Medicine  
Philadelphia, PA, USA*

**WILEY Blackwell**

This edition first published 2022  
© 2022 John Wiley & Sons Ltd

#### *Edition History*

*John Wiley & Sons Ltd (1e, 2006);*

*John Wiley & Sons Ltd (2e, 2013)*

All rights reserved. No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, recording or otherwise, except as permitted by law. Advice on how to obtain permission to reuse material from this title is available at <http://www.wiley.com/go/permissions>.

The right of Brian L. Strom, Stephen E. Kimmel, Sean Hennessy to be identified as the authors of the editorial material in this work has been asserted in accordance with law.

#### *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

For details of our global editorial offices, customer services, and more information about Wiley products visit us at [www.wiley.com](http://www.wiley.com).

Wiley also publishes its books in a variety of electronic formats and by print-on-demand. Some content that appears in standard print versions of this book may not be available in other formats.

#### *Limit of Liability/Disclaimer of Warranty*

The contents of this work are intended to further general scientific research, understanding, and discussion only and are not intended and should not be relied upon as recommending or promoting scientific method, diagnosis, or treatment by physicians for any particular patient. In view of ongoing research, equipment modifications, changes in governmental regulations, and the constant flow of information relating to the use of medicines, equipment, and devices, the reader is urged to review and evaluate the information provided in the package insert or instructions for each medicine, equipment, or device for, among other things, any changes in the instructions or indication of usage and for added warnings and precautions. While the publisher and authors have used their best efforts in preparing this work, they make no representations or warranties with respect to the accuracy or completeness of the contents of this work and specifically disclaim all warranties, including without limitation any implied warranties of merchantability or fitness for a particular purpose. No warranty may be created or extended by sales representatives, written sales materials or promotional statements for this work. The fact that an organization, website, or product is referred to in this work as a citation and/or potential source of further information does not mean that the publisher and authors endorse the information or services the organization, website, or product may provide or recommendations it may make. This work is sold with the understanding that the publisher is not engaged in rendering professional services. The advice and strategies contained herein may not be suitable for your situation. You should consult with a specialist where appropriate. Further, readers should be aware that websites listed in this work may have changed or disappeared between when this work was written and when it is read. Neither the publisher nor authors shall be liable for any loss of profit or any other commercial damages, including but not limited to special, incidental, consequential, or other damages.

#### *Library of Congress Cataloging-in-Publication Data*

Names: Strom, Brian L., editor. | Kimmel, Stephen | Hennessy, Sean, editor.  
E., editor.

Title: Textbook of pharmacoepidemiology / edited by Brian L. Strom, Sean Hennessy, Stephen E. Kimmel.

Description: Third edition. | Hoboken, NJ : Wiley-Blackwell, 2021. |

Includes bibliographical references and index.

Identifiers: LCCN 2021029285 (print) | LCCN 2021029286 (ebook) | ISBN 9781119701071 (paperback) | ISBN 9781119701088 (adobe pdf) | ISBN 9781119701118 (epub)

Subjects: MESH: Pharmacoepidemiology--methods

Classification: LCC RM302.5 (print) | LCC RM302.5 (ebook) | NLM QV 771 | DDC 615.7/042--dc23

LC record available at <https://lcn.loc.gov/2021029285>

LC ebook record available at <https://lcn.loc.gov/2021029286>

Cover Design: Wiley

Cover Image: © Shutterstock/Getty Images r.classen/Shutterstock

Set in 9.5/12.5pt STIXTwoText by Straive, Pondicherry, India

## Contents

<b>Contributors</b>	<i>xvii</i>
<b>Preface</b>	<i>xxi</i>
<b>Acknowledgements</b>	<i>xxv</i>

### Part I Introduction to Pharmacoepidemiology 1

#### 1 What is Pharmacoepidemiology? 3

*Brian L. Strom*

Introduction 3

Definition of Pharmacoepidemiology 3

Pharmacoepidemiology Versus Clinical Pharmacology 4

Pharmacoepidemiology Versus Epidemiology 5

Historical Background 5

Early Legislation 5

Drug Crises and Resulting Regulatory Actions 7

Legislative Actions Resulting from Drug Crises 9

Intellectual Development of Pharmacoepidemiology Emerging from Drug Crises 10

The Current Drug Approval Process 13

Drug Approval in the US 13

Drug Approval in Other Countries 14

Potential Contributions of Pharmacoepidemiology 15

Supplementary Information 16

New Types of Information Not Available from Premarketing Studies 17

General Contributions of Pharmacoepidemiology 17

Key Points 18

Further Reading 18

#### 2 Study Designs Available for Pharmacoepidemiologic Studies 20

*Brian L. Strom*

Introduction 20

Overview of the Scientific Method 20

Types of Errors that one Can Make in Performing a Study 22

Criteria for the Causal Nature of an Association 23

Epidemiologic Study Designs 26

Case Reports 26

Case Series 26

Analyses of Secular Trends	27
Case–Control Studies	28
Cohort Studies	28
Analysis of Case–Control and Cohort Studies	29
Randomized Clinical Trials	30
Discussion	31
Conclusion	32
Key Points	32
Further Reading	33
<b>3 Sample Size Considerations for Pharmacoepidemiologic Studies</b>	<b>35</b>
<i>Brian L. Strom</i>	
Introduction	35
Sample Size Calculations for Cohort Studies	35
Sample Size Calculations for Case–Control Studies	40
Sample Size Calculations for Case Series	41
Discussion	43
Key Points	45
Further Reading	45
<b>4 Basic Principles of Clinical Pharmacology Relevant to Pharmacoepidemiologic Studies</b>	<b>47</b>
<i>Jeffrey S. Barrett</i>	
Introduction	47
Clinical Pharmacology and Pharmacoepidemiology	48
Basics of Clinical Pharmacology	48
Pharmacokinetics	49
Absorption	49
Volume of Distribution	49
Metabolism	49
Elimination	51
Special Populations	52
Elderly	52
Pediatrics	53
Pregnancy	55
Organ Impairment	55
Drug Interactions	56
Pharmacodynamics	56
Overview	57
Pharmacogenomics	59
Model-Informed Drug Development	59
Conclusion	60
Key Points	60
Further Reading	61
<b>5 When Should One Perform Pharmacoepidemiologic Studies?</b>	<b>62</b>
<i>Brian L. Strom</i>	
Introduction	62
Reasons to Perform Pharmacoepidemiologic Studies	62



Regulatory	63
Marketing	64
Legal	65
Clinical	66
Safety Versus Risk	67
Risk Tolerance	67
Features of the Adverse Outcome	68
Characteristics of the Exposure	68
Perceptions of the Evaluator	69
Conclusion	70
Key Points	70
Further Reading	71

## **6 Views from Academia, Industry, Regulatory Agencies, and the Legal System 73**

*Joshua J. Gagne, Jerry Avorn, Nicolle M. Gatto, Jingping Mo, Gerald J. Dal Pan, June Raine, Shinobu Uzu, Aaron S. Kesselheim, and Kerstin N. Vokinger*

The View from Academia	73
Introduction	73
The Drug Approval Process	74
Prescribing Practices	75
Evaluation of Patients' Use of Drugs in the Health Care System	76
Assessment of the Quality and Outcomes of Medication Use in Populations	76
Policy Analysis	77
Interventional Pharmacoepidemiology	77
Economic Assessment of Medication-Related Issues	78
The Academic Medical Center	78
Consortia of Academic Medical Center Programs for Pharmacoepidemiologic Research	78
The Future	79
Summary Points for the View from Academia	79
The View from Industry	81
Introduction	81
Regulatory and Industry Focus on Risk Management and Epidemiology	81
Epidemiology in Drug Safety Evaluation	83
Epidemiology in Evaluation of Risk Mitigation Interventions	86
Conclusion	87
Summary Points for the View from Industry	88
The View from Regulatory Agencies	90
Introduction	90
Assessing the Need for Medicines	91
Orphan Drugs	91
Planning Drug Development Programs	92
Pre-approval Review of Clinical Safety Data	93
Planning for Post-approval Studies	94
Monitoring Post-approval Safety	94
Assessing Actual Use Patterns of a Medicine	95
Assessing Impact of Regulatory Actions	95
Advancing the Science of Pharmacoepidemiology	96

Conclusion	97
Summary Points for the View from Regulatory Agencies	97
The View from the Legal System	98
Introduction	98
Tort Law and Product Liability Lawsuits	98
Pharmacoepidemiology and Contract Law	102
Pharmacoepidemiology and Intellectual Property Law	103
Conclusion	105
Summary Points for the View from the Legal System	105
Further Reading	107
The View from Academia	107
The View from Industry	108
The View from Regulatory Agencies	109
The View from the Legal System	110
Contract-Related Issues in Pharmacoepidemiology	110
Patent Law and Pharmacoepidemiology	110

## **Part II Sources of Pharmacoepidemiology Data 113**

### **7 Postmarketing Spontaneous Pharmacovigilance Reporting Systems 115**

*Gerald J. Dal Pan, Marie Lindquist, and Kate Gelperin*

Introduction	115
Description	116
Adverse Events and Adverse Drug Reactions	116
Overview of Pharmacovigilance Reporting Systems	117
The Concept of Spontaneous AE/ADR Reporting	118
Report Characteristics	119
Social Media	121
National Pharmacovigilance Systems	121
National and International Postmarketing Adverse Event Databases	123
Detecting Signals from a Postmarketing Adverse Event Database	124
Review of Individual Case Safety Reports	126
Reporting Ratios	127
Strengths	128
Signal Detection	128
Opportunity for the Public to Report AEs/ADRs	129
Scope	129
Limitations	129
Quality of Reports	129
Underreporting	130
Non-uniform Temporal Trends in Reporting	130
Particular Applications	131
Case Series and Reporting Rates	131
Data Mining Signals	131
Signals from Developing Countries	131
The Future	132
Key Points	132
Further Reading	134

- 8 Overview of Electronic Databases in Pharmacoepidemiology** 136  
*Brian L. Strom*  
Introduction 136  
Description 137  
    Claims and Other Administrative Databases 137  
    Electronic Health Record Databases 138  
Strengths 138  
Weaknesses 139  
Particular Applications 140  
The Future 140  
Key Points 141  
Further Reading 141
- 9 Encounter Databases** 142  
*Tobias Gerhard, Yola Moride, Anton Pottegård, and Nicole Pratt*  
Introduction 142  
Description 142  
    Attributes of Encounter Databases 145  
    Selected Encounter Databases 149  
Strengths 161  
Limitations 162  
Particular Applications 163  
    Typical Activities Involved in Studies Using Encounter Databases 163  
    Deciding Between Individual Encounter Databases 164  
The Future 166  
Key Points 167  
Further Reading 171  
US Databases 172  
European Databases 172  
Canadian Databases 173  
Asian Databases 173
- 10 Electronic Health Record Databases** 174  
*Daniel B. Horton, Harshvinder Bhullar, Francesca Cunningham, Janet Sultana, and Gialuca Trifirò*  
Introduction 174  
Description 174  
    Overview of Health Care Systems and Populations 174  
    Overview of Databases 181  
    Data Collection and Structure 182  
    Data Quality: Accuracy and Completeness 183  
    Data Access for Researchers 184  
Strengths 184  
    Population-Based Data, Sample Size, and Length of Follow-up 184  
    Validity of Clinical Information 184  
    Accuracy of Drug Information 184  
    Ability to Access Original Health Records 184  
    Linkage to External Patient-Level Data 185

- Limitations 185
  - Incompleteness of Clinical Data 185
  - Incompleteness of Drug Data 185
- The Future 186
- Summary Points for Electronic Health Record Databases 187
- Acknowledgment 187
- Further Readings 189

## **11 Primary Data Collection for Pharmacoepidemiology 192**

*Priscilla Velentgas*

- Introduction 192
  - Research Questions that Require Primary Data 192
  - Hybrid or Enriched Designs 195
- Methods of Primary Data Collection 195
  - Site-Based Data Collection 195
  - Clinician or Site-Reported Outcomes (ClinROs) 195
  - Patient-Generated Data 196
  - Registries as Means of Data Collection 196
  - Biobanks/Specimen Banks 197
  - Guidelines on the Quality of Data Collection 197
- Strengths 197
- Limitations 197
- Particular Applications 198
- Conclusions 199
- Key Points 199
- Further Reading 201

## **12 How Should One Perform Pharmacoepidemiologic Studies?**

### **Choosing Among the Available Alternatives 203**

*Brian L. Strom*

- Introduction 203
- Choosing Among the Available Approaches to Pharmacoepidemiologic Studies 203
  - Comparative Characteristics of Pharmacoepidemiologic Data Resources 208
  - Characteristics of Research Questions and their Impact on the Choice of Pharmacoepidemiologic Data Resources 211
- Examples 215
- Conclusion 216
- Key Points 216
- Further Reading 216

## **Part III Special Issues in Pharmacoepidemiology Methodology 219**

## **13 Validity of Drug and Diagnosis Data in Pharmacoepidemiology 221**

*Mary Elizabeth Ritchey, Suzanne L. West, and George Maldonado*

- Introduction 221
- Clinical Problems to be Addressed by Pharmacoepidemiologic Research 221
- Methodological Problems to be Solved by Pharmacoepidemiologic Research 222
  - Indices of Measurement Error Relevant to Pharmacoepidemiologic Research 222

Quantitative Measurement of Validity	222
Quantitative Measurement of Reliability	224
Measurement Error in Pharmacoepidemiologic Research	225
Adjusting Measures of Association for Measurement Error	227
Self-Reported Drug Data from Ad hoc Survey Studies: Recall Accuracy	228
The Influence of Medication Class	228
The Influence of Questionnaire Design	228
The Influence of Patient Population	229
Self-Reported Diagnosis and Hospitalization Data from Ad hoc Studies: Recall Accuracy	230
The Influences of Medical Condition Type	230
The Influences of Timing of Diagnosis and Its Emotional Effects on the Patient	230
The Influence of Patient Population	232
The Influence of Questionnaire Design	232
Currently Available Solutions	233
Following Best Practices for Questionnaire Design	233
Developing a De novo Questionnaire	233
Conducting Validation Studies to Assess Self-Reported Data	235
Considering the Influence of Comparator Selection on Validation Studies	235
Validation of Pharmacoepidemiologic Drug and Diagnosis Data from Electronic Encounter Databases	236
Special Considerations with Drug Data	237
Special Considerations with Diagnosis and Hospitalization Data	237
Special Considerations with Distributed Data Systems	239
Best Practices	239
The Future	242
Key Points	242
Further Reading	243
<b>14 Assessing Causality from Case Reports</b>	<b>246</b>
<i>Bernard Bégaud and Judith K. Jones</i>	
Introduction	246
Clinical Problems to be Addressed by Pharmacoepidemiologic Research	246
The Two Paradigms of Causality Assessment	246
When is Assessing Causation from Cases Reports Useful?	247
Spontaneous Reporting	247
Clinical Trials and Pharmacoepidemiology	248
Clinical Practice and Prescription	248
Reports of Adverse Drug Reactions to Medical Journals	248
Hypothesis Generation and Research	248
Methodological Problems to be Addressed by Pharmacoepidemiologic Research	248
Approaches for Assessing Causation from Individual Cases	249
Expert Judgment/Global Introspection	249
Structured Guidelines and Algorithms	250
Probabilistic Approaches	251
Calibration	253
Choosing the Appropriate Approach	253
The Future	254
Key Points	255
Further Reading	255

<b>15 Molecular Pharmacoepidemiology</b>	257
<i>Christine Y. Lu and Stephen E. Kimmel</i>	
Introduction	257
Definitions and Concepts	258
Genetic Variability	258
Pharmacogenetics and Pharmacogenomics	259
The Interface of Pharmacogenetics and Pharmacogenomics with Molecular Pharmacoepidemiology	259
Clinical Problems to be Addressed by Pharmacoepidemiologic Research	260
Three Ways That Genes Can Affect Drug Response	260
The Interplay of Various Mechanisms	263
The Progression and Clinical Application of Molecular Pharmacoepidemiology	264
Methodological Problems to be Addressed by Pharmacoepidemiologic Research	264
Interactions	266
Type I Error	267
Type II Error	267
Confounding by Population Admixture	268
Currently Available Solutions	269
Identifying Additional Genetic Contributions to Drug Response	269
Interactions	270
Type I Error and Replication	270
Type II Error	271
Confounding by Population Admixture	271
The Future	271
Key Points	273
Further Reading	274
<b>16 Bioethical Issues in Pharmacoepidemiologic Research</b>	276
<i>Laura E. Bothwell, Annika Richterich, and Jeremy Greene</i>	
Introduction	276
Clinical Problems to be Addressed by Pharmacoepidemiologic Research	276
The Emergence, Changing Methods, and Moral Stakes of Pharmacoepidemiology in Twentieth Century North America	276
European Pharmacoepidemiologic Trends and Ethics	280
East Asian Pharmacoepidemiologic Trends and Ethics	282
Methodologic Problems to be Solved by Pharmacoepidemiologic Research	283
Informed Consent	284
Ethics of Surveillance	285
Ethical Benefits of Pharmacoepidemiologic Research for Data Integrity	285
Problems of Conflicts of Interest for Drug Industry Research	286
Currently Available Solutions	286
Good Pharmacoepidemiology and Pharmacovigilance Practices	286
Protections against Conflicts of Interest for Drug Industry-Sponsored Research	288
The Future	289
Acknowledgement	291
Key Points	291
Further Reading	293

- 17 The Use of Randomized Controlled Trials for Pharmacoepidemiology** 294  
*Samuel M. Lesko, Allen A. Mitchell, and Robert F. Reynolds*  
 Introduction 294  
 Clinical Problems to be Addressed by Pharmacoepidemiologic Research 294  
 Methodological Problems to be Solved by Pharmacoepidemiologic Research 296  
   Overview of Classic RCTs 296  
   Limitations of RCTs 298  
 Currently Available Solutions 298  
 Large Simple Trials 298  
   When is an LST Feasible? 301  
   Logistics of Conducting an LST 302  
 Analysis 303  
 Primary Analysis 303  
   Subgroup Analyses 303  
   Data Monitoring/Interim Analyses 304  
 The Future 304  
 Key Points 305  
 Further Reading 305
- 18 Pharmacoeconomics: Economic Evaluation of Pharmaceuticals** 307  
*Kevin A. Schulman*  
 Introduction 307  
 Clinical Problems to be Addressed by Pharmacoeconomic Research 307  
   The Economics of Drug Development 307  
   Health Economics and Health Care Financing 308  
 Methodological Problems to be Addressed by Pharmacoeconomic Research 312  
   Types of Analysis 312  
   Types of Costs 315  
   Perspective of Analysis 316  
   Using Economic Data 317  
 The Future 320  
 Acknowledgements 320  
 Key Points 320  
 Further Reading 320
- 19 Patient Engagement and Patient Reported Outcomes** 322  
*Esi M. Morgan and Adam C. Carle*  
 Introduction 322  
 Patient Reported Outcomes in Clinical Trials 323  
 Patient Reported Outcomes in Routine Care 323  
 Patient Reported Outcomes as Motivation to Develop New Therapeutic Strategies 325  
 Clinical Problems to be Addressed by Pharmacoepidemiologic Research 326  
   Ensuring PRO Completion and Results Review 326  
   PRO Selection, Score Interpretation and Interventions 326  
   Patient Engagement and Individualized Assessment and Treatment Plans 327  
   Barriers to Measuring PROs in Clinical Practice and Using PROs to Guide Interventions 327

Methodologic Problems to be Solved by Pharmacoepidemiologic Research	328
Currently Available Solutions	328
Discordance in Perspectives between Patients, Clinicians and Researchers	328
Measuring within Person Change	329
Selection of Patient Reported Outcomes and Implementation into Practice	330
The Future	330
Key Points	331
Further Reading	331
<b>20 The Use of Meta-analysis in Pharmacoepidemiology</b>	<b>334</b>
<i>Brenda J. Crowe, Stephen J.W. Evans, H. Amy Xia, and Jesse A. Berlin</i>	
Introduction	334
Clinical Problems to be Addressed by Pharmacoepidemiologic Research	335
Methodological Problems to be Solved by Pharmacoepidemiologic Research	336
Susceptibility of the Original Studies to Bias	336
Combinability of Studies	336
Publication Bias	337
Bias in the Abstraction of Data	338
Currently Available Solutions	338
Steps Involved in Performing a Meta-analysis	338
Publication Bias	344
Indirect Comparison and Simultaneous Comparison of Treatments Available for Specific Conditions	346
Case Studies of Applications of Meta-analysis	346
The Future	350
Key Points	351
Further Reading	352
<b>21 Studies of Medication Adherence</b>	<b>355</b>
<i>Julie Lauffenburger, Trisha Acri, and Robert Gross</i>	
Introduction	355
Clinical Problems to be Addressed by Pharmacoepidemiologic Research	356
Methodological Problems to be Addressed by Pharmacoepidemiologic Research	357
Currently Available Solutions	357
Analysis Issues in Adherence	362
Use of Adherence Data in Clinical Trials and Comparative Effectiveness Studies	362
Selecting Adherence Intervals	362
Statistical Analysis	363
Time-Varying Nature of Adherence and Trajectory Modeling	364
Prediction of Adherence for Interventions	365
The Future	365
Key Points	365
Further Reading	366
<b>22 Advanced Approaches to Controlling Confounding in Pharmacoepidemiologic Studies</b>	<b>368</b>
<i>Sebastian Schneeweiss and Samy Suissa</i>	
Introduction	368



Clinical Problems to be Addressed by Pharmacoepidemiologic Research	368
Methodological Problems to be Addressed by Pharmacoepidemiologic Research	368
Currently Available Solutions	370
Efficient Sampling Designs within a Cohort Study	370
Analytic Approaches for Improved Confounding Control	377
Conclusion	382
Key Points	382
Further Reading	384

## **Part IV Special Applications and the Future of Pharmacoepidemiology 387**

### **23 Special Applications of Pharmacoepidemiology 389**

*David Lee, Björn Wettermark, Christine Y. Lu, Stephen B. Soumerai, Robert T. Chen, Sharon-Lise T. Normand, Art Sedrakyan, Danica Marinac-Dabic, Daniel B. Horton, Sonia Hernandez-Diaz, Tamar Lasky, Krista F. Huybrechts, Claudia Manzo, Emil Cochino, Hanna M. Seidling, David W. Bates, Bennett Levitan, Rachael L. DiSantostefano, and Scott Evans*

Studies of Drug Utilization 389

Introduction 389

    Clinical Problems to be Addressed by Pharmacoepidemiologic Research 391

    Methodological Problems to be Addressed by Pharmacoepidemiologic Research 392

    Examples of Currently Available Solutions 393

    The Future 396

    Key Points for Studies of Drug Utilization 396

Evaluating and Improving Prescribing 398

    Clinical Problems to be Addressed by Pharmacoepidemiologic Research 398

    Methodological Problems to be Addressed by Pharmacoepidemiologic Research 398

    Examples of Currently Available Solutions 399

    The Future 402

    Key Points for Evaluating and Improving Prescribing 402

Special Methodological Issues in Pharmacoepidemiologic Studies of Vaccine Safety 403

    Clinical Problems to be Addressed by Pharmacoepidemiologic Research 403

    Methodological Problems to be Addressed by Pharmacoepidemiologic Research 404

    Examples of Currently Available Solutions 407

    The Future 408

    Key Points for Special Methodological Issues in Pharmacoepidemiologic Studies of Vaccine Safety 408

Epidemiologic Studies of Implantable Medical Devices 408

    What Is a Medical Device and how Is it Different from a Drug? 409

    Clinical Problems to be Addressed by Medical Device Epidemiologic Research 409

    Methodological Problems to be Solved by Medical Device Epidemiologic Research 410

    Examples of Currently Available Solutions 412

    The Future 415

    Key Points for Epidemiologic Studies of Devices 418

Research on the Effects of Medications in Pregnancy and in Children 418

    Clinical Problems to be Addressed by Pharmacoepidemiologic Research 418

    Methodological Problems to be Solved by Pharmacoepidemiologic Research 419

Examples of Currently Available Solutions	423
The Future	424
Key Points for Research on the Effects of Medications in Pregnancy and in Children	426
Risk Management	427
Clinical Problems to be Addressed by Pharmacoepidemiologic Research	428
Methodological Problems to be Addressed by Pharmacoepidemiologic Research	433
Examples of Currently Available Solutions	434
The Future	434
Key Points for Risk Management	436
The Pharmacoepidemiology of Medication Errors	436
Safety Theory	436
Patient Safety Concepts as Applied to Pharmacoepidemiology	437
Clinical Problems to be Addressed by Pharmacoepidemiologic Research	438
Methodological Problems to be Addressed by Pharmacoepidemiologic Research	441
The Future	442
Key Points for the Pharmacoepidemiology of Medication Errors	442
Benefit–Risk Assessments of Medical Treatments	442
Clinical Problems to be Addressed by Pharmacoepidemiologic Research	443
Methodological Problems to be Addressed by Pharmacoepidemiologic Research	443
Examples of Currently Available Solutions	444
The Future	451
Key Points for Benefit–Risk Assessments of Medical Treatments	454
Further Reading	454
<b>24 The Future of Pharmacoepidemiology</b>	<b>464</b>
<i>Brian L. Strom, Stephen E. Kimmel, and Sean Hennessy</i>	
Introduction	464
The View from Academia	465
Scientific Developments	465
Funding	469
Personnel	470
The View from Industry	471
The View from Regulatory Agencies	472
The View from the Law	473
Conclusion	473
Key Points	473
Further Reading	474
<b>Appendix A – Sample Size Tables</b>	<b>475</b>
<b>Appendix B – Glossary</b>	<b>493</b>
<b>Index</b>	<b>505</b>

## List of Contributors

### ***Trisha Acri***

Department of Family and Community  
Medicine Temple University School of  
Medicine Philadelphia, PA, USA  
Currently, Director of Community Research  
Health Services, AIDS Care Group, AIDS Care  
Group, Sharon Hill, PA, USA

### ***Jerry Avorn***

Harvard Medical School and Brigham and  
Women's Hospital  
Boston, MA, USA

### ***Jeffrey S. Barrett***

Critical Path Institute  
Tucson, AZ, USA

### ***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***

Clinical Pharmacology and  
Pharmacoepidemiology, Medical School  
University of Bordeaux  
Bordeaux, France

### ***Jesse A. Berlin***

Johnson & Johnson  
Titusville, NJ, USA

### ***Harshvinder Bhullar***

Independent Consultant London, UK

### ***Laura E. Bothwell***

Yale School of Public Health  
New Haven, Connecticut, USA

### ***Adam C. Carle***

Cincinnati Children's Hospital Medical Center  
Cincinnati, OH, USA  
University of Cincinnati, College of Medicine  
Cincinnati, OH, USA  
University of Cincinnati, College of  
Arts and Sciences  
Cincinnati, OH, USA

### ***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***

US Department of Veterans Affairs  
Hines, IL, 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

***Rachael L. DiSantostefano***

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

***Scott Evans***

Biostatistics Center  
The George Washington University  
Rockville, MD, USA

***Stephen J.W. Evans***

The London School of Hygiene and Tropical  
Medicine, London, UK

***Joshua J. Gagne***

Harvard Medical School and Brigham and  
Women's Hospital, Boston, MA, USA  
and  
Johnson and Johnson  
New Brunswick, NJ, USA

***Nicolle M. Gatto***

Aetion 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***

Ernest Mario School of Pharmacy  
Rutgers Biomedical and Health Sciences  
Piscataway, NJ, USA  
and  
Center for Pharmacoepidemiology and  
Treatment Science  
Rutgers Biomedical and Health Sciences  
New Brunswick, NJ, USA

***Jeremy Greene***

Johns Hopkins University  
Baltimore, Maryland, MD, USA

***Robert Gross***

Center for Clinical Epidemiology and  
Biostatistics

Center for Pharmacoepidemiology Research  
and Training, Perelman School of Medicine  
University of Pennsylvania, Philadelphia  
PA, USA

***Sean Hennessy***

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

***Sonia Hernandez Diaz***

Harvard T.H. Chan School of Public Health  
Boston, MA, USA

***Daniel B. Horton***

Rutgers Robert Wood Johnson  
Medical School, Rutgers Center for  
Pharmacoepidemiology and Treatment  
Science, Rutgers School of Public Health  
New Brunswick, NJ, USA

***Krista F. Huybrechts***

Brigham and Women's Hospital  
Harvard Medical School  
Boston, MA, USA

***Judith K. Jones***

†Formerly Principal Consultant PharmaLex,  
Inc., Fairfax, VA and Adjunct Faculty  
The University of Michigan School of Public  
Health Summer Program  
Ann Arbor, USA

***Aaron S. Kesselheim***

Harvard Medical School and Brigham and  
Women's Hospital  
Boston, MA, USA

***Stephen E. Kimmel***

University of Florida College of Public  
Health and Health Professions & College of  
Medicine  
Gainesville, FL, USA

***Tamar Lasky***

US Food and Drug Administration  
Silver Spring, MD, USA

**Julie Lauffenburger**

Brigham and Women's Hospital and Harvard  
Medical School  
Boston, MA, USA

**David Lee**

Center for Pharmaceutical Management  
Management Sciences for Health  
Arlington, VA, USA

**Samuel M. Lesko**

Northeast Regional Cancer Institute and  
Geisinger Commonwealth School of Medicine  
Scranton, PA, USA

**Bennett Levitan**

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

**Marie Lindquist**

Uppsala Monitoring Centre  
WHO Collaborating Centre for International  
Drug Monitoring  
Uppsala, Sweden

**Christine Y. Lu**

Harvard Medical School and Harvard Pilgrim  
Health Care Institute, Boston, MA, USA

**George Maldonado**

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

**Claudia Manzo**

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

**Danica Marinac-Dabic**

Division of Epidemiology  
Office of Surveillance and Biometrics Center  
for Devices and Radiological Health  
US Food and Drug Administration  
Silver Spring, MD, USA

**Allen A. Mitchell**

Slone Epidemiology Center at Boston  
University, Boston, MA, USA

**Jingping Mo**

Epidemiology, Worldwide Research &  
Development, Pfizer Inc.  
New York, NY, USA

**Esi M. Morgan**

Seattle Children's Hospital  
Seattle, WA, USA  
University of Washington  
Seattle, WA, USA

**Yola Moride**

Center for Pharmacoepidemiology and  
Treatment Science, Rutgers Biomedical and  
Health Sciences  
New Brunswick, NJ, USA

**Sharon-Lise T. Normand**

Harvard Medical School and  
Harvard School of Public Health  
Boston, MA, USA

**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, Clinical and Health Sciences  
University of South Australia, Adelaide,  
South Australia, Australia

**June Raine**

Vigilance and Risk Management of Medicine  
Medicines and Healthcare Products  
Regulatory Agency, London, UK

**Robert F. Reynolds**

Epidemiology, Research and Development,  
GlaxoSmithKline, New York, NY, USA

***Annika Richterich***

Maastricht University  
Maastricht, The Netherlands

***Mary Elizabeth Ritchey***

Med Tech Epi, LLC, Philadelphia, PA, USA  
Center for Pharmacoepidemiology and  
Treatment Science, Rutgers University  
New Brunswick, NJ, USA

***Sebastian Schneeweiss***

Departments of Medicine and Epidemiology  
Harvard Medical School and  
Division of Pharmacoepidemiology  
Department of Medicine  
Brigham & Women's Hospital  
Boston, MA, USA

***Kevin A. Schulman***

Clinical Excellence Research Center  
Stanford University  
Stanford, CA, USA

***Art Sedrakyan***

Department of Public Health  
New York Presbyterian Hospital and  
Weill Cornell Medical College  
New York, NY, USA

***Hanna M. Seidling***

Head of Cooperation Unit Clinical Pharmacy  
Department of Clinical Pharmacology and  
Pharmacoepidemiology Cooperation Unit  
Clinical Pharmacy  
University of Heidelberg  
Heidelberg, Germany

***Stephen B. Soumerai***

Department of Population Medicine Director  
Drug Policy Research Group  
Harvard Medical School and Harvard Pilgrim  
Health Care Institute  
Boston, MA, USA

***Brian L. Strom***

Rutgers Biomedical and Health Sciences  
Newark, NJ, USA

***Samy Suissa***

McGill University and Jewish General Hospital  
Montreal, Quebec, Canada

***Janet Sultana***

Mater Dei Hospital, Msida, Malta  
and Exeter College of Medicine and Health  
University of Exeter, Exeter, UK

***Gianluca Trifiro***

Department of Diagnostics and Public Health  
University of Verona, Verona, Italy

***Shinobu Uzu***

Pharmaceuticals and Medical Devices Agency  
Tokyo, Japan

***Priscilla Velentgas***

Real World Solutions, IQVIA, Inc.  
Cambridge, MA, USA

***Kerstin N. Vokinger***

Harvard Medical school and Brigham and  
Women's Hospital  
Boston, MA, USA  
and  
Institute for Law University of Zurich  
Zurich, Switzerland

***Suzanne L. West***

Gillings School of Global Public Health  
University of North Carolina  
Chapel Hill, NC, USA

***Björn Wettermark***

Disciplinary Domain of Medicine and Pharmacy  
Uppsala University, Uppsala, Sweden

***H. Amy Xia***

Amgen, Thousand Oaks  
CA, USA

## Preface

It was a remarkable 33 years ago that the first edition of Strom's *Pharmacoepidemiology* was published. The preface to that book stated that pharmacoepidemiology was a new field with a new generation of pharmacoepidemiologists arising to join the field's few pioneers. Over the ensuing 32 years, the field indeed has grown and no longer deserves to be called "new." Many of those "new generation" scientists (including two of the editors of this book) are now "middle-aged" pharmacoepidemiologists. Despite its relatively brief academic life, a short history of pharmacoepidemiology and review of its current state will set the stage for the purpose of this textbook.

Pharmacoepidemiology originally arose from the union of the fields of clinical pharmacology and epidemiology. Pharmacoepidemiology studies the use of and the effects of medical products in large numbers of people and applies the methods of epidemiology to the content area of clinical pharmacology. This field represents the science underlying post-marketing medical product surveillance, studies of the effects of medical products (i.e. drugs, biologicals, devices) performed after a product has been approved for use. In recent years, pharmacoepidemiology has expanded to include many other types of studies, as well.

The field of pharmacoepidemiology has grown enormously since the first publication of Strom. The International Society of Pharmacoepidemiology, an early idea when the first edition of this book 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 scientific 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 as well. We have also become institutionalized as a subfield within the field of clinical pharmacology, with scientific sections of 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, pharmacoconomics, and quality-of-life studies. The continuing parade of drug safety crises emphasizes 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 evaluation and mitigation

strategies are now required by regulatory bodies with the marketing of new drugs, as a means of improving drugs' benefit/risk balance, and manufacturers are identifying ways to respond. Requirements that a drug be proven to be cost effective have been added to many 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 personnel. Pharmacoepidemiologic research funding is now more plentiful, and even limited support for training is 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, the utility of drug utilization review programs is being questioned. In addition, the Joint Commission requires that every hospital in the US 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 to conduct.

In recent years, major new changes have been made in drug regulation and organization, largely in response to a series of accusations about myocardial infarction caused by analgesics, which was detected in long-term prevention trials rather than in normal use of the drugs. For example, FDA was given new regulatory authority after drug marketing. Further, the development, since 1 January 2006, of Medicare Part D, a US federal program to subsidize prescription drugs for Medicare

recipients, introduced to pharmacoepidemiology a new database with a stable population approaching 50 million in what may be the largest healthcare system in the world. The US Congress has recognized the importance of the field, with the founding of the Sentinel Program, and new requirements that FDA focus on "real world evidence." A new movement has arisen in the US of "comparative effectiveness research," which in many ways learns from much longer experience in Europe, as well as decades of experience in pharmacoepidemiology. These developments portend major changes for our field.

In summary, there has been tremendous growth in the field of pharmacoepidemiology and a fair amount of maturation. With the growth and maturation of the field, Strom's *Pharmacoepidemiology* has grown and matured right along. *Pharmacoepidemiology* thus represents a comprehensive source of information about the field. As a reflection of the growth of the field, the fourth Edition of Strom was over twice as long as the first! Now, seven years after the fifth edition, the field continues to change and garner widespread interest, leading to the recent publication of the sixth edition in 2020.

So, why, one may ask, do we need a Textbook of Pharmacoepidemiology? The need arose precisely because of the growth of the field. With that, and the corresponding growth in the parentbook, Strom's *Pharmacoepidemiology* has really become more of a reference book than a book usable as a textbook. Yet, there is increasing need for people to be trained in the field and an increasing number of training programs. With the maturity of the field comes therefore the necessity for both comprehensive approaches (such as Strom's *Pharmacoepidemiology*) and more focused approaches. Therefore, *Textbook of Pharmacoepidemiology* was intended as a modified and shortened version of its parent, designed to meet the need of students. We believe that students can benefit from an approach that focuses on the core of the discipline, along with learning aids.



*Textbook of Pharmacoepidemiology* attempts to fill this need, providing a focused educational resource for students. It is our hope that this book will serve as a useful textbook for students at all levels: upper-level undergraduates, graduate students, post-doctoral fellows, and others who are learning the field. To achieve our goals, we have substantially edited down from Strom's *Pharmacoepidemiology*, with a focus on what is needed by students, eliminating some chapters and shortening others. We also have provided case examples for most chapters and key points for all chapters. Each chapter is followed by a list of further reading.

So why update it? In looking at the sixth Edition of Strom, most chapters in the new edition were thoroughly revised to provide updated content. New chapters were added, along with many new authors. The second edition of the textbook was simply getting out of date in comparison to the recently published sixth edition of the parent book.

Specifically, we have tried to emphasize the methods of pharmacoepidemiology and the strengths and limitations of the field, while minimizing some of the technical specifications that are important for a reference book but not for students. Therefore, the first five chapters of Part I, "Introduction to Pharmacoepidemiology," lay out the cores of the discipline, and remain essentially unchanged from Strom's *Pharmacoepidemiology*, with the exception of the inclusion of key points and lists of further reading. We have also included a chapter on different perspectives of the field (from academia, industry, regulatory agencies, and the legal system), as a shortened form of several chapters from the reference book. Part II focuses on "Sources of Pharmacoepidemiology

Data" and includes important chapters about spontaneous pharmacovigilance reporting systems, electronic databases, and other approaches to pharmacoepidemiology studies. Part III summarizes "Special Issues in Pharmacoepidemiology Methodology" that we feel are important to more advanced pharmacoepidemiology students. Although no student is likely to become an expert in all of these methods, they form a core set of knowledge that we believe all pharmacoepidemiologists should have. In addition, one never knows what one will do later in one's own career, nor when one may be called upon to help others with the use of these methods. Part IV concludes the textbook with a collection of "Special Applications" of the field, and speculation about its future, always an important consideration for new investigators in charting a career path.

Pharmacoepidemiology may be maturing, but many exciting opportunities and challenges lie ahead as the field continues to grow and respond to unforeseeable future events. It is our hope that this book can continue to serve as a useful introduction and resource for students of pharmacoepidemiology, both those enrolled in formal classes and those learning in "the real world," who will respond to the challenges that they encounter. Of course, we are always students of our own discipline, and the process of developing this textbook has been educational for us. We hope that this book will also be stimulating and educational for you.

Brian L. Strom, MD, MPH.  
Stephen E. Kimmel, MD, MSCE.  
Sean Hennessy, PharmD, PhD.  
January 2022



## Acknowledgments

There are many individuals and institutions to whom we owe thanks for their contributions to our efforts in preparing this book. Mostly, we would like to thank all of the contributors for the work that they did in revising their book chapters and sections for this textbook and providing case examples, key points, and suggested readings. Over the years, our pharmacoepidemiology work has been supported mostly by numerous grants from government, foundations, and industry. While none of this support was specifically intended to support the development of this book, without this assistance, we would not have been able to support our careers in pharmacoepidemiology. We would like to thank our publisher, John Wiley & Sons, Ltd., for their assistance and insights, both in support of this book, and in support of the field's journal, *Pharmacoepidemiology and Drug Safety*.

John Hemphill's contributions to this book were instrumental, encompassing the role of project manager where he coordinated the entire process of contacting the authors and pulling the book together, while additionally providing editorial assistance.

BLS would like to thank Steve Kimmel and Sean Hennessy for joining him as co-editors. Steve did the bulk of the work on the first edition of this textbook, and Steve and Sean joined BLS as co-editors for the fifth and sixth edition of the parent book, *Pharmacoepidemiology*. These are two very special and talented men. It has been BLS's pleasure to help train them – now, too many years ago – help them cultivate

their own careers, and see them blossom into star senior pharmacoepidemiologists. It is 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 parents, now deceased, for the support and education that were critical to him being successful in his career. BLS would also like to thank the late Paul D. Stolley, M.D., M.P.H. and the late Kenneth L. Melmon, M.D., for their direction, guidance, and inspiration in the formative years of his career. He would also 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 its earlier editions, for the kids), 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 SH for all of his years as an amazing colleague, 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 during the many late evenings that SEK 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 to Pharmacoepidemiology**

