

Adam LaCaze  
Barbara Osimani *Editors*

---

# Uncertainty in Pharmacology

Epistemology, Methods, and Decisions

# **Boston Studies in the Philosophy and History of Science**

Volume 338

## **Editors**

Alisa Bokulich, Boston University

Jürgen Renn, Max Planck Institute for the History of Science

Michela Massimi, University of Edinburgh

## **Managing Editor**

Lindy Divarci, Max Planck Institute for the History of Science

## **Editorial Board**

Theodore Arabatzis, University of Athens

Heather E. Douglas, University of Waterloo

Jean Gayon, Université Paris 1

Thomas F. Glick, Boston University

Hubert Goenner, University of Goettingen

John Heilbron, University of California, Berkeley

Diana Kormos-Buchwald, California Institute of Technology

Christoph Lehner, Max Planck Institute for the History of Science

Peter McLaughlin, Universität Heidelberg

Agustí Nieto-Galan, Universitat Autònoma de Barcelona

Nuccio Ordine, Università della Calabria

Sylvan S. Schweber, Harvard University

Ana Simões, Universidade de Lisboa

John J. Stachel, Boston University

Baichun Zhang, Chinese Academy of Science

The series *Boston Studies in the Philosophy and History of Science* was conceived in the broadest framework of interdisciplinary and international concerns. Natural scientists, mathematicians, social scientists and philosophers have contributed to the series, as have historians and sociologists of science, linguists, psychologists, physicians, and literary critics.

The series has been able to include works by authors from many other countries around the world.

The editors believe that the history and philosophy of science should itself be scientific, self-consciously critical, humane as well as rational, sceptical and undogmatic while also receptive to discussion of first principles. One of the aims of *Boston Studies*, therefore, is to develop collaboration among scientists, historians and philosophers.

*Boston Studies in the Philosophy and History of Science* looks into and reflects on interactions between epistemological and historical dimensions in an effort to understand the scientific enterprise from every viewpoint.

More information about this series at <http://www.springer.com/series/5710>

Adam LaCaze • Barbara Osimani  
Editors

# Uncertainty in Pharmacology

Epistemology, Methods, and Decisions

 Springer

*Editors*

Adam LaCaze  
School of Pharmacy  
The University of Queensland  
St Lucia, QLD, Australia

Barbara Osimani  
Department of Biomedical Sciences  
and Public Health  
Polytechnic University of the Marche  
Ancona, Italy  
Munich Center for Mathematical  
Philosophy  
Munich, LMU  
Munich, Germany

ISSN 0068-0346

ISSN 2214-7942 (electronic)

Boston Studies in the Philosophy and History of Science

ISBN 978-3-030-29178-5

ISBN 978-3-030-29179-2 (eBook)

<https://doi.org/10.1007/978-3-030-29179-2>

© Springer Nature Switzerland AG 2020

This work is subject to copyright. All rights are reserved by the Publisher, whether the whole or part of the material is concerned, specifically the rights of translation, reprinting, reuse of illustrations, recitation, broadcasting, reproduction on microfilms or in any other physical way, and transmission or information storage and retrieval, electronic adaptation, computer software, or by similar or dissimilar methodology now known or hereafter developed.

The use of general descriptive names, registered names, trademarks, service marks, etc. in this publication does not imply, even in the absence of a specific statement, that such names are exempt from the relevant protective laws and regulations and therefore free for general use.

The publisher, the authors, and the editors are safe to assume that the advice and information in this book are believed to be true and accurate at the date of publication. Neither the publisher nor the authors or the editors give a warranty, expressed or implied, with respect to the material contained herein or for any errors or omissions that may have been made. The publisher remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

This Springer imprint is published by the registered company Springer Nature Switzerland AG.  
The registered company address is: Gewerbestrasse 11, 6330 Cham, Switzerland

# Preface

Pharmacology is the science of drug action. Combined with other biomedical sciences, it underpins clinical drug development, drug regulation and clinical use of drugs and informs broader interactions between drugs and society. Many deep and practically important philosophical questions arise in this domain: How should pharmacological theories be understood? How should diverse lines of evidence in the biological, medical and clinical sciences be amalgamated to inform the care of individuals? How should drugs be evaluated and regulated? What is the appropriate role of the pharmaceutical industry? to name just a few. Work from the philosophy of biology, epistemology, philosophy of science, philosophy of medicine and ethics is relevant to these questions. In recent years, the quantity of work that engages with the practice and specific problems that arise in pharmacology and the use of drugs has increased. This work examines the foundations, methods and values of clinical and experimental pharmacology and contributes to our understanding of the science and its implementation in clinical and regulatory decision-making. This volume seeks to showcase the depth and breadth of work broadly characterised as philosophy of pharmacology and to present it within a single volume for the first time.

The contributions are diverse in terms of the disciplinary backgrounds of the authors, topics and methodological approaches. The volume contains work from philosophers, clinicians, regulators and statisticians. Some tackle practical issues as they arise within their discipline, while others take a more theoretical focus. The topics range from the appropriate way to think about evidence of mechanisms in clinical medicine to the normative foundations of pharmaceutical regulation, taking in inference patterns when evaluating the effects of drugs, the role of values in pharmacology and the history of masking treatment allocation in clinical trials along the way. Contributions are presented according to the following topic themes: EPISTEMOLOGY; METHODS; and DECISIONS. The methodological approach of many of the contributions fits under the broad umbrella of analytical philosophy. Some of the methods employed include the in-depth exploration of a case (Bueter and Jukola, Chap. 20), historical analysis (Holman, Chap. 17) and formal epistemology (Poellinger and Landes, Chaps. 5 and 11).

The role of mechanisms and evidence of mechanisms in medicine is an important topic in the philosophy of pharmacology and one that many of the contributions in this volume touch on. The first four chapters in the EPISTEMOLOGY section explore this topic. Aronson provides a clinical pharmacologist's perspective on the definition of "mechanism" and then differentiates two types of relation between mechanisms and evidence: evidence of mechanisms, which he labels "evidence-based mechanism", and the use of mechanisms as evidence, "mechanism-based evidence". The distinction highlights the different ways that mechanisms are discussed and used in pharmacology and clarifies some aspects of the debate regarding the role of mechanisms in evidence-based decision-making. Rocca, Anjum and Mumford take a different perspective, focusing on how mechanistic knowledge can develop in cases of *causal failure*. Causal failure occurs when the treatment fails to deliver the expected outcome. They also argue that instances of causal failure provide an opportunity to learn more about the context-sensitive, intrinsic, tendential and complex mechanisms by which drugs produce effects.

The next two chapters explore the role that mechanisms play in extrapolation. Parkkinen and Williamson compare strategies for extrapolating causal claims from model organisms to humans using atherosclerosis research as a case study. They argue that evidence of mechanisms plays an important role in the key strategies employed when extrapolating from model organisms: comparative process tracing, phylogenetic reasoning and robustness analysis. The importance of evidence of mechanisms to these strategies, they argue, provides further support for the Russo-Williamson thesis—the epistemological claim that evidence of mechanisms and evidence of difference-making are typically needed in order to establish causal claims. Belzung, Bilette de Villemeur and Lemoine provide an analysis of drug development in psychiatry to argue for a different set of conclusions regarding extrapolation from animal models. Belzung and colleagues argue that the use of previously successful animal models in the development of psychopharmacology frequently relies on a form of *statistical extrapolation* and that the received view of extrapolation tends to underestimate the importance of this kind of extrapolation.

The remaining chapters in the EPISTEMOLOGY section examine a range of theoretical and practical topics regarding pharmacological knowledge. Poellinger seeks to illustrate and distinguish analogy-based inference patterns in the causal assessment of drug harms. Boem, Malagrìno and Bertolaso examine the role of *in silico* clinical trials in addressing complexity in pharmacology. Sözüdoğru and Clarke examine the use of Lipinski's rule of five as a heuristic strategy within drug discovery and explore what this means for standard mechanistic and capacity accounts of causation. And finally, Ruthenberg completes the section with a discussion of underdetermination in chemistry and pharmacology.

Contributions within the METHODS section examine the role and limits of randomised trials and the challenge of reliable biomarkers and consider a range of approaches to amalgamating pharmacological evidence produced by different methods. The first two chapters in this section explore the logic of randomised trials. Festa, Tambolo and Cevolani suggest that the principles governing the assessment of efficacy hypotheses, and, more generally, hypotheses of statistical causality,

are provided by an appropriate statistical version of the method of difference put forward by John Stuart Mill. Annoni and Boniolo examine assumptions regarding specific and non-specific treatment effects and question the commonly held view that these effects are additive and easily separated for the purposes of efficacy assessment.

The contributions from Landes and LaCaze and Winckel look at the application of evidence hierarchies. Landes approaches the problem of ranking drugs for a particular outcome using diverse lines of evidence as a multi-criteria decision problem. This chapter employs the formal machinery of decision sciences to provide a ranking of drugs based on the available evidence. Using metformin-associated lactic acidosis as a case study, LaCaze and Winckel argue that a causal approach to drug safety assessment along the lines of the Russo-Williamson thesis is superior to the method-focussed approach advocated within evidence-based medicine.

The next two chapters explore methods to reduce uncertainty in clinical trials. Keyser and Sarry analyse the methodological use of clinical biomarkers in pharmacological measurement. Their contribution presents a systematic methodology for assessing the reliability of multiple biomarkers underpinned by robustness analysis. Mansmann and Boulesteix continue this theme by examining four standard statistical methods to reduce and model uncertainty about individual response to treatments. Mansmann and Boulesteix propose ways to improve the analysis and presentation of heterogeneous treatment outcomes. Osimani's contribution closes the second part of the volume and introduces the last one by addressing (implicit) strategic dimensions related to how evidence is gathered, evaluated and used. The chapter analyses the dissent around evidence standards in medicine and pharmacology as a result of distinct ways to address epistemic losses and to conceptualise reliability in distinct scientific paradigms and philosophical schools of thought.

The final section, DECISIONS, considers the relations between science, policy and regulatory decision-making. Hansson begins the section with a consideration of the appropriate role of non-epistemic values in pharmacological science. The next four chapters approach pharmaceutical regulation, pharmaceutical markets and the influence of industry and society more broadly. Holman discusses the development of standards for assessing therapeutic claims and the contribution of the American Medical Association's Council on Pharmacy and Chemistry on a growing pharmaceutical market prior to the establishment of the US Food and Drug Administration. Teira examines two normative principles that underpin pharmaceutical regulation: a liberal argument for protecting pharmaceutical markets in terms of quality control and a paternalistic argument for protecting consumers of medicines. Teira argues for a paternalistic approach to pharmaceutical regulation based on the need for *impartial* information regarding the benefits and harms of medicines. Solomon's contribution considers the issue of industry bias and offers both qualitative and quantitative proposals to reduce the impact of this bias. Bueter and Jukola close out the volume with an analysis of the FDA's decision to approve flibanserin as a treatment for a "hypoactive sexual desire disorder". Bueter and Jukola suggest that criticising the approval of flibanserin primarily in terms



of medicalisation is problematic and argue in favour of institutional rather than conceptual safeguards against unnecessary pharmaceutical medicalisation.

We would like to thank the contributors for submitting their work, the reviewers for their contribution to the volume and the editorial team at Springer for their assistance. It has been a pleasure to put together this volume. We believe it well illustrates the breadth of work in the emerging subdiscipline of philosophy of pharmacology.

Funding for the research and editorial work by Barbara Osimani has been provided through the ERC funded project: “Philosophy of Pharmacology: Safety, Statistical Standards, and Evidence Amalgamation” – PhilPharm GA 639276.

Brisbane, Australia  
Ancona, Italy  
May 2019

Adam LaCaze  
Barbara Osimani

# Contents

## Part I Epistemology

<b>1</b>	<b>Defining Aspects of Mechanisms: Evidence-Based Mechanism (Evidence <i>for</i> a Mechanism), Mechanism-Based Evidence (Evidence <i>from</i> a Mechanism), and Mechanistic Reasoning</b> .....	3
	Jeffrey K. Aronson	
<b>2</b>	<b>Causal Insights from Failure: Post-marketing Risk Assessment of Drugs as a Way to Uncover Causal Mechanisms</b> .....	39
	Elena Rocca, Rani Lill Anjum, and Stephen Mumford	
<b>3</b>	<b>Extrapolating from Model Organisms in Pharmacology</b> .....	59
	Veli-Pekka Parkkinen and Jon Williamson	
<b>4</b>	<b>Mechanistic vs Statistical Extrapolation in Preclinical Research in Psychiatry: Challenging the Received View</b> .....	79
	Catherine Belzung, Etienne Billette de Villemeur, and Maël Lemoine	
<b>5</b>	<b>Analogy-Based Inference Patterns in Pharmacological Research</b> .....	101
	Roland Poellinger	
<b>6</b>	<b>In Silico Clinical Trials: A Possible Response to Complexity in Pharmacology</b> .....	135
	Federico Boem, Ilaria Malagrino, and Marta Bertolaso	
<b>7</b>	<b>Uncertainty in Drug Discovery: Strategies, Heuristics and Technologies</b> .....	153
	Erman Sözüdoğru and Brendan Clarke	
<b>8</b>	<b>“Caught in the Amber”: A Sketch of Chemical Underdetermination</b> .....	173
	Klaus Ruthenberg	

## Part II Methods

- 9 A Millian Look at the Logic of Clinical Trials**..... 187  
Roberto Festa, Gustavo Cevolani, and Luca Tambolo
- 10 Learning by Difference: Placebo Effects and Specific Efficacy  
in Pharmacological RCTs** ..... 211  
Marco Annoni and Giovanni Boniolo
- 11 An Evidence-Hierarchical Decision Aid for Ranking  
in Evidence-Based Medicine**..... 231  
Jürgen Landes
- 12 Assessing Drug Safety Assessment: Metformin Associated  
Lactic Acidosis** ..... 261  
Adam LaCaze and Karl Winckel
- 13 Robust Biomarkers: Methodologically Tracking Causal  
Processes in Alzheimer’s Measurement** ..... 289  
Vadim Keyser and Louis Sarry
- 14 Modelling Individual Response to Treatment and Its  
Uncertainty: A Review of Statistical Methods and Challenges  
for Future Research** ..... 319  
Ulrich Mansmann and Anne-Laure Boulesteix
- 15 Epistemic Gains and Epistemic Games: Reliability and Higher  
Order Evidence in Medicine and Pharmacology**..... 345  
Barbara Osimani

## Part III Decisions

- 16 Values in Pharmacology** ..... 375  
Sven Ove Hansson
- 17 Humbug, the Council of Pharmacy and Chemistry,  
and the Origin of “The Blind Test” of Therapeutic Efficacy** ..... 397  
Bennett Holman
- 18 On the Normative Foundations of Pharmaceutical Regulation** ..... 417  
David Teira
- 19 After Disclosure**..... 439  
Miriam Solomon
- 20 Sex, Drugs, and How to Deal with Criticism: The Case  
of Flibanserin** ..... 451  
Anke Bueter and Saana Jukola

# List of Contributors

**Rani Lill Anjum** Norwegian University of Life Sciences (NMBU), Ås, Norway

**Marco Annoni** National Research Council, Rome, Italy  
National Institute of Biomedical Technologies, Milan, Italy  
Fondazione Umberto Veronesi, Milan, Italy

**Jeffrey K. Aronson** Centre for Evidence Based Medicine, Nuffield Department of Primary Care Health Sciences, Radcliffe Observatory Quarter, Oxford, UK

**Catherine Belzung** University of Tours, INSERM U930, Tours, France

**Marta Bertolaso** Università Campus Bio-Medico di Roma, Rome, Italy

**Etienne Billette de Villemeur** University of Lille, LEM (UMR CNRS 9221), Lille, France

**Federico Boem** University of Milan, Milan, Italy

**Giovanni Boniolo** Dipartimento di Scienze Biomediche e Chirurgico Specialistiche, Università di Ferrara, Ferrara, Italy  
Institute for Advanced Study, Technische Universität München, Munich, Germany

**Anne-Laure Boulesteix** Institute for Medical Informatics, Biometry and Epidemiology, Ludwig-Maximilians Universität München, Munich, Germany

**Anke Bueter** Leibniz University Hannover, Hannover, Germany

**Gustavo Cevolani** IMT School for Advanced Studies Lucca, Lucca, Italy  
Center for Logic, Language, and Cognition, University of Turin, Turin, Italy

**Brendan Clarke** Department of Science and Technology Studies, UCL, London, UK

**Roberto Festa** Department of Humanistic Studies, University of Trieste, Trieste, Italy

**Sven Ove Hansson** Division of Philosophy, Royal Institute of Technology (KTH), Stockholm, Sweden  
Department of Learning, Informatics, Management and Ethics, Karolinska Institutet, Solna, Sweden

**Bennett Holman** Underwood International College, Yonsei University, Seoul, South Korea  
Faculty of Humanities, University of Johannesburg, Johannesburg, South Africa

**Saana Jukola** Bielefeld University, Bielefeld, Germany

**Vadim Keyser** California State University, Fresno, CA, USA

**Adam LaCaze** School of Pharmacy, The University of Queensland, Brisbane, QLD, Australia

**Jürgen Landes** Munich Center for Mathematical Philosophy, LMU Munich, Munich, Germany

**Maël Lemoine** University of Bordeaux, Immunoconcept, Bordeaux, France

**Iaria Malagrino** Università Campus Bio-Medico di Roma, Rome, Italy

**Stephen Mumford** Durham University, Durham, UK

**Ulrich Mansmann** Institute for Medical Informatics, Biometry and Epidemiology, Ludwig-Maximilians Universität München, Munich, Germany

**Barbara Osimani** Department of Biomedical Sciences and Public Health, Polytechnic University of the Marche, Ancona, Italy  
Munich Center for Mathematical Philosophy, München, LMU, Munich, Germany

**Veli-Pekka Parkkinen** Department of Philosophy, University of Bergen, Bergen, Norway

**Roland Poellinger** Department of Arts and Culture of the City of Munich, Munich, Germany

**Elena Rocca** Norwegian University of Life Sciences (NMBU), Ås, Norway

**Klaus Ruthenberg** Coburg University of Applied Sciences and Arts, Coburg, Germany

**Louis Sarry** California State University, Fresno, CA, USA

**Miriam Solomon** Temple University, Philadelphia, PA, USA

**Erman Sözüdoğru** Department of Science and Technology Studies, UCL, London, UK

**Luca Tambolo** Department of Humanistic Studies, University of Trieste, Trieste, Italy

**David Teira** Universidad Nacional de Educación, Madrid, Spain

**Jon Williamson** Centre for Reasoning, University of Kent, Canterbury, UK

**Karl Winckel** School of Pharmacy, The University of Queensland, Brisbane, QLD,  
Australia  
Princess Alexandra Hospital, Brisbane, QLD, Australia