

Pharmacogenetics of Psychotropic Drugs

Pharmacogenetics and pharmacogenomics are areas of rapidly growing importance at the interface of molecular genetics and psychopharmacology, with implications for drug development and clinical practice. This book provides a conceptual framework for understanding and studying the pharmacogenetics of psychotropic drugs; it reviews advances in the field and describes the findings that have already emerged.

Coverage extends to antipsychotics, antidepressants, mood-stabilizing, cognitive-enhancing, and anxiolytic drugs. Chapters also examine the interface of pharmacogenetics with substance dependence and brain imaging, and consider the impact of pharmacogenetics on the biotechnology and pharmaceutical industries.

This book defines the young field of pharmacogenetics as it applies to psychotropic drugs and is, therefore, an essential reference for all clinicians and researchers working in this field.

Bernard Lerer is Professor of Psychiatry and Director of the Biological Psychiatry Laboratory at Hadassah-Hebrew University Medical Center in Jerusalem. He is Director of the National Institute for Psychobiology in Israel, and Editor-in-Chief of the *International Journal of Neuropsychopharmacology*.

Cambridge University Press
978-0-521-18961-3 - Pharmacogenetics of Psychotropic Drugs
Edited by Bernard Lerer
Frontmatter
[More information](#)

Pharmacogenetics of Psychotropic Drugs

Edited by

Bernard Lerer

Hadassah-Hebrew University Medical Center, Jerusalem, Israel



CAMBRIDGE
UNIVERSITY PRESS

Cambridge University Press
978-0-521-18961-3 - Pharmacogenetics of Psychotropic Drugs
Edited by Bernard Lerer
Frontmatter
[More information](#)

CAMBRIDGE UNIVERSITY PRESS
Cambridge, New York, Melbourne, Madrid, Cape Town,
Singapore, São Paulo, Delhi, Tokyo, Mexico City

Cambridge University Press
The Edinburgh Building, Cambridge CB2 8RU, UK

Published in the United States of America by Cambridge University Press, New York

www.cambridge.org
Information on this title: www.cambridge.org/9780521189613

© Cambridge University Press 2002

This publication is in copyright. Subject to statutory exception and to the provisions of relevant collective licensing agreements, no reproduction of any part may take place without the written permission of Cambridge University Press.

First published 2002
First paperback edition 2011

A catalogue record for this publication is available from the British Library

Library of Congress Cataloguing in Publication data

Pharmacogenetics of psychotropic drugs / edited by Bernard Lerer.
p. cm.

Includes bibliographical references and index.

ISBN 0 521 80617 8 (hbk.)

1. Psychotropic drugs. 2. Pharmacogenetics. I. Lerer, Bernard.

RM315.P446 2002

615'.788-dc21 2001043946

ISBN 978-0-521-80617-6 Hardback

ISBN 978-0-521-18961-3 Paperback

Additional resources for this publication at www.cambridge.org/9780521189613

Cambridge University Press has no responsibility for the persistence or accuracy of URLs for external or third-party internet websites referred to in this publication, and does not guarantee that any content on such websites is, or will remain, accurate or appropriate.

Every effort has been made in preparing this book to provide accurate and up-to-date information that is in accord with accepted standards and practice at the time of publication. Although case histories are drawn from actual cases, every effort has been made to disguise the identities of the individuals involved. Nevertheless, the authors, editors, and publishers can make no warranties that the information contained herein is totally free from error, not least because clinical standards are constantly changing through research and regulation. The authors, editors, and publishers therefore disclaim all liability for direct or consequential damages resulting from the use of material contained in this book. Readers are strongly advised to pay careful attention to information provided by the manufacturer of any drugs or equipment that they plan to use.

Contents

List of contributors *page viii*

Part I Introduction

- 1 Genes and psychopharmacology: exploring the interface 3
Bernard Lerer

Part II Clinical background and research design

- 2 From pharmacogenetics to pharmacogenomics of psychotropic drug 21
response
Anil K. Malhotra
- 3 Neuropsychopharmacology: the interface between genes and psychiatric 36
nosology
Thomas A. Ban
- 4 Methodological issues in psychopharmacogenetics 57
Sheldon H. Preskorn
- 5 Statistical approaches in psychopharmacogenetics 72
Fabio Macciardi

Part III Molecular background

- 6 The psychopharmacogenetic–neurodevelopmental interface in serotonergic 95
gene pathways
K. Peter Lesch, Jens Benninghoff, and Angelika Schmitt

v

vi **Contents**

- 7 RNA processing regulation and interindividual variation 127
 Colleen M. Niswender and Linda K. Hutchinson

Part IV Pharmacokinetics

- 8 Pharmacogenetics of psychotropic drug metabolism 157
 Vural Ozdemir, Angela D.M. Kashuba, Vincenzo S. Basile, and James L. Kennedy
- 9 Pharmacogenetics of chiral psychotropic drugs 181
 Pierre Baumann and Chin B. Eap

Part V Specific psychotropic drugs and disorders

- 10 Clozapine response and genetic variation in neurotransmitter receptor targets 217
 David A. Collier, Maria J. Arranz, Sarah Osborne, Katherine J. Aitchison, Janet Munro, Dalu Mancama, and Robert W. Kerwin
- 11 Genetic factors underlying drug-induced tardive dyskinesia 245
 Ronnen H. Segman and Bernard Lerer
- 12 Functional gene-linked polymorphic regions in pharmacogenetics 267
 Marco Catalano
- 13 Alternative phenotypes and the pharmacogenetics of mood and anxiety disorders 283
 Emanuela Mundo and James L. Kennedy
- 14 Pharmacogenetics of anxiolytic drugs and the GABA-benzodiazepine receptor complex 300
 Smita A. Pandit, Spilios V. Argyropoulos, Patrick G. Kehoe, and David J. Nutt
- 15 Genetic factors and long-term prophylaxis in bipolar disorder 320
 Martin Alda
- 16 Genetic influences on responsiveness to anticonvulsant drugs 333
 Thomas N. Ferraro
- 17 Apolipoprotein E as a marker in the treatment of Alzheimer's disease 360
 Keith Schappert, Pierre Sevigny, and Judes Poirier

vii **Contents**

- 18 Genetic variation and drug dependence risk factors 372
Joel Gelernter and Henry Kranzler

Part VI **Pharmacogenetics and brain imaging**

- 19 Brain imaging and pharmacogenetics in Alzheimer's disease and
schizophrenia 391
Steven G. Potkin, James L. Kennedy, and Vincenzo S. Basile

Part VII **Industry perspectives**

- 20 Pharmacogenetics in psychotropic drug discovery and development 401
William Z. Potter, AnnCatherine Van Lone, and Larry Altstiel
- 21 High-throughput single nucleotide polymorphism genotyping 420
Anne Shalom and Ariel Darvasi
- Index* 439

Contributors

Martin Alda

Department of Psychiatry, Dalhousie University, Abbie J. Lane Building, 5909 Jubilee Rd, Halifax, Nova Scotia, B3H 2E2, Canada

Larry Altsteil

Schering-Plough Research Institute, 2015 Galloping Hill Rd, Kenilworth, NJ 07033-1300, USA

Spilios V. Argyropoulos

Psychopharmacology Unit, University of Bristol, University Walk, Bristol BS8 1TD, UK

Maria J. Arranz

Institute of Psychiatry, De Crespigny Park, Denmark Hill, London SE5 8AF, UK

Thomas A. Ban

Vanderbilt University, Nashville, TN, USA

Vincenzo S. Basile

Neurogenetics Section, Centre for Addiction and Mental Health, University of Toronto, Toronto, Canada

Pierre Baumann

Department Universitaire de Psychiatrie Adulte, Adulte Hopital de Cery, CH-1008 Prilly, Switzerland

Jens Benninghoff

Department of Psychiatry, University of Wurzburg, Fuchsleinstr. 15, 97080 Wurzburg, Germany

Marco Catalano

IRCCS H. San Raffaele, Department of Neuropsychiatric Sciences, Milan, Italy

David A. Collier

Institute of Psychiatry, De Crespigny Park, Denmark Hill, London SE5 8AF, UK

Ariel Darvasi

The Life Sciences Institute, The Hebrew University of Jerusalem and IDgene Pharmaceuticals, Jerusalem 91904, Israel

Chin B. Eap

Department Universitaire de Psychiatrie Adulte, Adulte Hopital de Cery, CH-1008 Prilly, Switzerland

Thomas N. Ferraro

Center for Neurobiology and Behavior, Department of Psychiatry, University of Pennsylvania School of Medicine, 415 Curie Blvd, Philadelphia, PA 19104, USA

ix **List of contributors**

Joel Gelernter

Department of Psychiatry, Yale University
School of Medicine, New Haven, CT 06516,
USA

Linda K. Hutchinson

Department of Pharmacology, Vanderbilt
University, Nashville, TN 37232, USA

Angela D.M. Kashuba

School of Pharmacy, University of North
Carolina, Chapel Hill, NC, USA

Patrick G. Kehoe

Psychopharmacology Unit, University of
Bristol, University Walk, Bristol, BS8 1TD,
UK

James L. Kennedy

Neurogenetics Section, Centre for Addiction
and Mental Health, University of Toronto,
Toronto, Canada

Robert W. Kerwin

Institute of Psychiatry, De Crespigny Park,
Denmark Hill, London SE5 8AF, UK

Henry Kranzler

Department of Psychiatry, University of
Connecticut, School of Medicine,
Farmington, CT, USA

Bernard Lerer

Biological Psychiatry Laboratory,
Department of Psychiatry, Hadassah-
Hebrew University Medical Center, Ein
Karem, Jerusalem 91120, Israel

K. Peter Lesch

Department of Psychiatry, University of
Wurzburg, Fuchsleinstr. 15, 97080
Wurzburg, Germany

Fabio Macciardi

Unit of Biostatistics and Genetic
Epidemiology, Neurogenetics Section,
Clarke Division, Center for Addiction and
Mental Health, R-32, 250 College Street,
Toronto, Ontario, M5T 1R8, Canada

Anil K. Malhotra

Unit of Molecular Psychiatry, Hillside
Hospital, 75–59 263rd St, Glen Oaks, NY
11004, USA

Dalu Mancama

Institute of Psychiatry, De Crespigny Park,
Denmark Hill, London SE5 8AF, UK

Emanuela Mundo

Department of Psychiatry, University of
Wurzburg, Fuchsleinstr. 15, 97080
Wurzburg, Germany

Janet Munro

Institute of Psychiatry, De Crespigny Park,
Denmark Hill, London SE5 8AF, UK

Colleen M. Niswender

Department of Pharmacology, University of
Washington, Seattle, WA 98195, USA

David J. Nutt

Psychopharmacology Unit, University of
Bristol, University Walk, Bristol, BS8 1TD,
UK

Sarah Osborne

Institute of Psychiatry, De Crespigny Park,
Denmark Hill, London SE5 8AF, UK

Vural Ozdemir

Department of Pharmacogenomics, Drug
Discovery Division, R.W. Johnson
Pharmaceutical Research Institute, Route
202 South, #1000 OMP Building, Raritan,
NJ 08869, USA

x **List of contributors**

Smita A. Pandit

Psychopharmacology Unit, University of
Bristol, University Walk, Bristol, BS8 1TD,
UK

Judes Poirier

Center for Studies in Aging, 6875 Blvd.
Lasalle, Verdun, Quebec, H4H 1R3, Canada

Steven G. Potkin

Brain Imaging Center, University of
California, Irvine Hall, Irvine, CA
92697–3960, USA

William Z. Potter

Lilly Research Laboratory, Lilly Corporate
Center, Drop Code 0532, Indianapolis, IA
46285, USA

Sheldon H. Preskorn

Psychiatric Research Institute, University of
Kansas, 1100 N. St Francis, Wichita, KS
67214, USA

Keith Schappert

Mirador DNA Design, Suite 501, 404 McGill
St, Montreal, Quebec H2Y 2G1, Canada

Angelina Schmitt

Department of Psychiatry, University of
Wurzburg, Fuchsleinstr. 15, 97080
Wurzburg, Germany

Ronnen H. Segman

Biological Psychiatry Laboratory,
Department of Psychiatry, Hadassah-
Hebrew University Medical Center, Ein
Karem, Jerusalem 91120, Israel

Pierre Savigny

Mirador DNA Design, Suite 501, 404 McGill
St, Montreal, Quebec H2Y 2G1, Canada

Anne Shalom

The Life Sciences Institute, The Hebrew
University of Jerusalem, Israel

AnnCatherine Van Lone

Lilly Research Laboratory, Lilly Corporate
Center, Drop Code 0532, Indianapolis, IA
46285, USA