Handbook of Drug–Nutrient Interactions

NUTRITION ◊ AND ◊ HEALTH

Adrianne Bendich, Series Editor

Handbook of Drug–Nutrient Interactions, edited by **Joseph I. Boullata and Vincent T. Armenti,** 2004

Nutrition and Oral Medicine, edited by **Riva Touger-Decker, David A. Sirois, and Connie C. Mobley,** 2004

IGF, Nutrition, and Health, edited by **M. Sue Houston, Jeffrey M. P. Holly, and Eva L. Feldman,** 2004

Epilepsy and the Ketogenic Diet, edited by **Carl E. Stafstrom and Jong M. Rho,** 2004

Nutrition and Bone Health, edited by **Michael F. Holick and Bess Dawson-Hughes,** 2004

Diet and Human Immune Function, edited by **David A. Hughes, L. Gail Darlington, and Adrianne Bendich,** 2004

Beverages in Nutrition and Health, edited by **Ted Wilson and Norman J. Temple,** 2004

Handbook of Clinical Nutrition and Aging, edited by **Connie Watkins Bales and Christine Seel Ritchie,** 2004

Fatty Acids: Physiological and Behavioral Functions, edited by **David I. Mostofsky, Shlomo Yehuda, and Norman Salem, Jr.,** 2001

Nutrition and Health in Developing Countries, edited by **Richard D. Semba and Martin W. Bloem,** 2001

Preventive Nutrition: The Comprehensive Guide for Health Professionals, Second Edition, edited by **Adrianne Bendich and Richard J. Deckelbaum,** 2001

Nutritional Health: Strategies for Disease Prevention, edited by **Ted Wilson and Norman J. Temple**, 2001

Clinical Nutrition of the Essential Trace Elements and Minerals: The Guide for Health Professionals, edited by **John D. Bogden and Leslie M. Klevey**, 2000

Primary and Secondary Preventive Nutrition, edited by **Adrianne Bendich and Richard J. Deckelbaum**, 2000

The Management of Eating Disorders and Obesity, edited by **David J. Goldstein**, 1999

Vitamin D: Physiology, Molecular Biology, and Clinical Applications, edited by **Michael F. Holick**, 1999

Preventive Nutrition: The Comprehensive Guide for Health Professionals, edited by **Adrianne Bendich and Richard J. Deckelbaum**, 1997

Handbook of Drug–Nutrient Interactions

Edited by

Joseph I. Boullata, PharmD

Temple University School of Pharmacy, Philadelphia, PA

and

Vincent T. Armenti, MD, PhD

Temple University School of Medicine, Philadelphia, PA

Foreword by

Margaret Malone, PhD, FCCP

Albany College of Pharmacy, Albany, NY

SPRINGER SCIENCE+BUSINESS MEDIA, LLC

Originally published by Humana Press Inc. in 2004
Softcover reprint of the hardcover 1st edition 2004

www.humanapr.com

Production Editor: Robin B. Weisberg
Cover design by Patricia F. Cleary.

This publication is printed on acid-free paper. ∞
ANSI Z39.48-1984 (American National Standards Institute) Permanence of Paper for Printed Library Materials.

10 9 8 7 6 5 4 3 2 1

Additional material to this book can be downloaded from http://extras.springer.com

Library of Congress Cataloging-in-Publication Data

Handbook of drug-nutrient interactions / edited by Joseph I. Boullata, and Vincent T. Armenti ; foreword by Margaret Malone.
p. ; cm. -- (Nutrition and health)
Includes bibliographical references and index.
ISBN 978-1-4757-5359-2 ISBN 978-1-59259-781-9 (eBook)
DOI 10.1007/978-1-59259-781-9
1. Drug-nutrient interactions--Handbooks, manuals, etc.
I. Boullata, Joseph I. II. Armenti, Vincent T. III. Series: Nutrition and health (Totowa, N.J.)
[DNLM: 1. Food-Drug Interactions--Handbooks. 2. Nutrition --Handbooks. QV 39 H23636 2004]

RM302.4.H355 2004

615'.70452--dc22 2003021008

Series Editor's Introduction

The *Nutrition and Health* series of books have an overriding mission to provide health professionals with texts that are considered essential because each includes (1) a synthesis of the state of the science; (2) timely, in-depth reviews by the leading researchers in their respective fields; (3) extensive, up-to-date, fully annotated reference lists; (4) a detailed index; (5) relevant tables and figures; (6) identification of paradigm shifts and the consequences; (7) virtually no overlap of information between chapters, but targeted, interchapter referrals; (8) suggestions of areas for future research; and (9) balanced, data-driven answers to patient/health professionals' questions that are based on the totality of evidence rather than the findings of any single study.

The series volumes are not the outcome of a symposium. Rather, each editor has the potential to examine a chosen area with a broad perspective, both in subject matter as well as in the choice of chapter authors. The international perspective, especially with regard to public health initiatives, is emphasized where appropriate. The editors, whose trainings are both research- and practice-oriented, have the opportunity to develop a primary objective for their book, define the scope and focus, and then invite the leading authorities from around the world to be part of their initiative. The authors are encouraged to provide an overview of the field, discuss their own research, and relate the research findings to potential human health consequences. Because each book is developed *de novo*, the chapters are coordinated so that the resulting volume imparts greater knowledge than the sum of the information contained in the individual chapters.

The *Handbook of Drug–Nutrient Interactions*, edited by Joseph I. Boullata and Vincent T. Armenti, is a critical addition to the *Nutrition and Health Series* and fully exemplifies the goals of the series. Both editors are internationally recognized leaders in the field of nutrition and drug therapy. Both are excellent communicators and have worked tirelessly to develop a book that is destined to be the benchmark in the field because of its extensive, in-depth chapters covering the most important aspects of the complex interactions between diet and its nutrient components, health status, developmental stage, growth, and aging and the effects of drugs. The editors have chosen 41 of the most well-recognized and respected authors from around the world to contribute the 26 informative chapters in the volume. Key features of this comprehensive volume include more than thirty extensive tables and figures that provide the reader with excellent sources of detailed information about drug–nutrient interactions.

The editors clearly understand the seriousness of the issue of drug–nutrient interactions. They have stated that "In the care of patients, both drug therapy and nutritional therapy are critical. The potential for drugs and nutrients to interact with each other is significant, but unrecognized by many clinicians. These interactions may result in therapeutic failure or adverse effects of the drug, or alterations in the nutritional status of the patient—in either case impacting the patient's outcome."

The book chapters are logically organized to provide the reader with all of the basics of both drug metabolism and nutrition in the first section, Overview of Drug–Nutrient Interactions. Unique chapters in this section include an introductory chapter that describes the basics of drug metabolism followed by a more in-depth chapter that includes a thorough discussion of the drug-metabolizing enzymes in the critical chapter that includes 325 references. There is also a comprehensive review of the basics of the metabolism of the major dietary nutrients.

Part II contains two chapters that examine the effects of either under- or overnutrition (obesity) on drug disposition and their effects. Specialized topics in the third section include the effects of concomitant consumption of foods and a drug and include a detailed description of Food and Drug Administration requirements for conducting a clinical study on a fasted or fed state. Non-nutritive components of the diet such as herbs, caffeine, charcoal broiling of foods, and alcohol also affect drug efficacy and these effects are presented in extensive tables that organize the data clearly for the reader. The effects of grapefruit juice, garlic, ginkgo and other key herbs as well as nutrient–nutrient interactions are reviewed in separate, comprehensive chapters.

Cutting-edge discussions of the roles of the major drugs used by patients are covered in individual chapters and related to the dietary factors that can either interfere with or enhance efficacy. Drugs affecting the cardiovascular system and the nervous system, with emphasis on antiepileptics, are reviewed in depth. Specific emphasis is given to the effects of dietary minerals on drug pharmacokinetics and pharmacodynamics depending on whether the individual is deficient in the specific mineral. Likewise, supplementation with various dietary factors including folate, vitamin D, vitamin K, and calcium is also included.

Of particular relevance to clinicians are the chapters in Part V that examine drug nutrient interactions by life stages. Chapters include infancy and childhood, pregnancy and lactation, and the elderly, stages that have special considerations when examining the types of drugs used by the different groups and the varied nutritional requirements of these life stages.

The final section looks at drug–nutrient interactions in individuals who have either chronic diseases or special needs for certain classes of drugs. The chapter on cancer patients is particularly sensitive to the potential for drugs to affect the precarious health balance in these patients. Transplant patients also have unique needs and this chapter contains a valuable table that provides details about the nutrient requirements of transplant patients posttransplant. Several chapters examine the effects of chronic infections including HIV, tuberculosis, and hepatitis. Another concentrates on the effects of autoimmune diseases including rheumatoid arthritis, diabetes, and lupus, the drugs used in treatment, and the interactions of the disease, drug, and nutritional status. The final chapter looks at the role of enteral nutrition in affecting drug delivery, disposition, and clearance, another important clinically focused chapter.

Of great importance, the editors and authors have provided chapters that balance the most technical information with discussions of its importance for clients and patients as well as graduate and medical students, health professionals, and academicians. Hallmarks of the chapters include complete definitions of terms with the abbreviation fully defined for the reader and consistent use of terms between chapters. There are numerous

relevant tables, graphs, and figures as well as up-to-date references; all chapters include a conclusion section that provides the highlights of major findings. The volume contains a highly annotated index and within chapters, readers are referred to relevant information in other chapters.

This important text provides practical, data-driven resources based on the totality of the evidence to help the reader evaluate the critical role of nutrition, especially in at-risk populations, in optimizing drug efficacy. The overarching goal of the editors is to provide fully referenced information to health professionals so they may have a balanced perspective on the value of foods and nutrients that are routinely consumed and how these can help to assure that drugs can deliver their maximum benefits with minimal adverse effects. Finally, it must be noted that all of the authors and the editors agree that much more research is required to be able to give the best advice to patients with regard to drug–nutrient interactions.

In conclusion, *Handbook of Drug–Nutrient Interactions* provides health professionals in many areas of research and practice with the most up-to-date, well-referenced, and easy-to-understand volume on the importance of nutrition in optimizing drug efficacy and avoiding adverse effects. This volume will serve the reader as the most authoritative resource in the field to date and is a very welcome addition to the *Nutrition and Health Series.*

Adrianne Bendich, *PhD, FACN*
Series Editor

Foreword

Although there is a great deal of literature regarding drug–nutrient interactions (DNIs), there are limited sources of up-to-date comprehensive information. The *Handbook of Drug–Nutrient Interactions* admirably fills this gap. The editors, Dr. Joseph I. Boullata and Dr. Vincent T. Armenti, have a wealth of experience in this therapeutic area and have assembled a fine cadre of chapter authors who have individually contributed their high level of expertise.

As treatment for many diseases becomes increasingly complex with multiple drug therapies scheduled at varying times, the need to identify clinically significant DNIs is an essential part of medication management. This is a shared responsibility between health care professionals to interpret available data and individualize an approach to therapy that is compatible with the patient's disease state, life stage, and dietary intake.

Awareness of the significance of drug–food interactions is generally lacking. Although many texts contain lengthy lists of possible interactions, few data are provided for the clinician to gain an understanding of the mechanism of action of the interaction and subsequently apply the information to a particular patient or group of patients. For example, in the management of patients with HIV-AIDS who are taking complex prescribed drug regimens, herbal products, and nutritional supplements, many of which are affected by dietary intake, careful attention to DNIs is a critical component of therapy. Clinicians need to take account of not only the well-documented interactions between drugs and nutrients, but also the less obvious effects on drug–nutrient disposition and metabolism. The current text provides the reader with this valuable insight.

Designing a regimen that is both safe and effective for the patient is an important part of collaborative drug therapy management. As such, this comprehensive handbook will serve as a resource for pharmacists, dietitians, nurses, and physicians as they partner to enable better drug therapy adherence and therapeutic outcomes for their patients. In addition, the *Handbook of Drug–Nutrient Interactions* will serve as an excellent resource for both educators and students in raising the level of awareness and knowledge of the mechanisms of DNIs such that their consideration is given a level of importance similar to that of drug–drug interactions, which are more consistently reviewed.

Margaret Malone, ***PhD, FCCP***
Department of Pharmacy Practice
Albany College of Pharmacy, Albany, NY

Preface

Although the influence of nutrition on health is obvious, its critical role in the care of patients is not as widely recognized. In caring for patients, more attention is often paid to the role of drug therapy. The field of clinical nutrition actually overlaps with the field of pharmacotherapy at several points, but none more clearly than at the interaction of drug and nutrient. A drug–nutrient interaction is considered the result of a physical, chemical, physiologic, or pathophysiologic relationship between a drug and nutrient(s)/food that is deemed significant when the therapeutic response is altered or the nutritional status compromised. We felt that a current reference book on this subject was long overdue, so we have put together this *Handbook of Drug–Nutrient Interactions.*

The handbook is intended for use by physicians, pharmacists, nurses, dietitians, nutritionists, and others, in training or in clinical practice, to better manage drug–nutrient interactions in their patients. This topic is particularly timely with so much attention being paid to the issue of patient safety in the current health care delivery system. Although a number of manuals exist that provide extensive lists of documented and potential drug–nutrient interactions, this handbook takes a scientific look behind many of those interactions, examines their relevance, gives recommendations, and suggests specific areas requiring research. This handbook provides clinicians with a guide for use in understanding, identifying, or predicting, and ultimately preventing or managing significant adverse drug–nutrient interactions to optimize patient care. We hope this handbook challenges clinicians to become more aware of potential drug–nutrient interactions, document them regularly, and carry out research projects to clarify their mechanisms and clinical significance. Much more needs to be known about drug–nutrient interactions than is currently appreciated. Some topics have yet to amass enough information to allow inclusion in a chapter; others are as yet unanticipated. For example, how long will it be before genetic engineering allows relatively inexpensive production of certain pharmaceuticals by plants? Without placing a value judgment on that notion, it becomes clear that the issue of drug–nutrient interactions has moved past the problems of how to time drug administration around meals.

The book begins with a perspective on the topic (Chapter 1), and is followed by overviews of drug disposition, nutrient disposition, and enzyme systems involved in both drug and nutrient metabolism (Chapters 2–4). These chapters allow the reader, regardless of discipline, to gain a sense of the topic and the underlying foundation that is needed in the remainder of the book. Two chapters discuss the effect of nutritional status on drug disposition and effect (Chapters 5–6), a topic often overlooked. The next group of chapters discusses the influence of food, nutrients, and non-nutrient dietary components on drug disposition and effect (Chapters 7–12). Given the widespread use of dietary supplements, interactions with drugs and with nutrients by this diverse group of substances—some of which behave more like drugs than nutrients—these chapters are most relevant. The influence of medications on nutrient status is presented both generally and in regard

to specific groups of drugs or nutrients (Chapters 13–17). Another set of chapters discusses drug–nutrient interactions that are relevant to various stages of the life cycle or to specific patient groups or conditions (Chapters 18–26).

There is no one best way to approach drug–nutrient interactions, and we have included some topics not typically considered in such a presentation. Clearly, not every documented drug–nutrient interaction identified in vitro, ex vivo, in animal models, or in human studies is covered. Not discussed are the sequential interactions between nutrients, disease and drugs (e.g., micronutrients impacting HIV disease, which then influences drug disposition). One multifaceted topic deserving of discussion, but not included, is the set of interactions involving parenteral nutrition, in terms of both the effect on drug disposition and the impact of each nutrient or combination of nutrients on each other and on concurrently infused drugs. However, parenteral drug–nutrient interactions could fill an entire book. Overlap is almost unavoidable in a book on drug–nutrient interactions, but we have tried to avoid major sections of redundancy. For example, although the chapter on interactions involving folate mentions the antiepileptics, a chapter entirely devoted to antiepileptic interactions follows. Similarly, the interactions involving grapefruit juice are touched on in several chapters, but a more in-depth discussion is reserved for the chapter dedicated to that topic. The more detailed chapter on the elderly is in part related to the historic relevance of drug–nutrient interactions in this group.

What we have attempted to provide is a bit more than a listing of common interactions. The authors, some having spent many years with their subject matter, provide a framework for understanding many of the more common, and some less common, drug–nutrient interactions, including the mechanisms and clinical approaches to their management. We hope that this *Handbook of Drug–Nutrient Interactions* helps make the case that the issue of drug–nutrient interactions is a significant one for clinicians and researchers alike. We are grateful to the authors for their work, and excited about this compilation, although we are looking forward to new information on drug–nutrient interactions as it continues to emerge. We would welcome comments from readers that will help improve the breadth, depth, and quality of this book and the care of patients.

Joseph I. Boullata, *PharmD*
Vincent T. Armenti, *MD, PhD*

Contents

Contributors

KARL E. ANDERSON, MD • *Departments of Preventive Medicine and Community Health, Internal Medicine, and Pharmacology and Toxicology, University of Texas Medical Branch, Galveston, TX*

VINCENT T. ARMENTI, MD, PhD • *Department of Surgery, Temple University School of Medicine, Philadelphia, PA*

DAVID G. BAILEY, BSc Pharm, PhD • *Department of Medicine and Lawson Health Research Institute, London Health Sciences Centre and Department of Physiology and Pharmacology, University of Western Ontario, London, Ontario, Canada*

JACQUELINE R. BARBER, PharmD, BCNSP • *Department of Pharmacy, Methodist Hospital Health Services, St. Louis Park, MN*

ADRIANNE BENDICH, PhD • *Medical Affairs, GlaxoSmithKline Consumer Healthcare, Parsippany, NJ*

MARY J. BERG, PharmD • *College of Pharmacy, University of Iowa, Iowa City, IA*

JOSEPH I. BOULLATA, PharmD, BCNSP • *Department of Pharmacy Practice, Temple University School of Pharmacy, Philadelphia, PA*

IMAD F. BTAICHE, PharmD, BCNSP • *College of Pharmacy, University of Michigan and Department of Pharmacy Services, University of Michigan Hospitals and Health Centers, Ann Arbor, MI*

TODD W. CANADA, PharmD, BCNSP • *Division of Pharmacy, The University of Texas M.D. Anderson Medical Center, Houston, TX*

LINGTAK-NEANDER CHAN, PharmD, BCNSP • *Colleges of Pharmacy and Medicine, University of Illinois at Chicago, Chicago, IL*

THOMAS K. H. CHANG, PhD • *Faculty of Pharmaceutical Sciences, University of British Columbia, Vancouver, British Columbia, Canada*

MARIANA CIFUENTES, PhD • *Instituto de Nutrición y Techcologia de los Alimentos, University of Chile, Santiago, Chile*

CHARLENE W. COMPHER, PhD, RD, FADA, CNSD • *School of Nursing, University of Pennsylvania, Philadelphia, PA*

LORI ENRIQUEZ, RD, CSP, CNSD • *Department of Clinical Nutrition, The Children's Hospital of Philadelphia, Philadelphia, PA*

DAVID FLEISHER, PhD • *Department of Pharmaceutical Sciences, College of Pharmacy, University of Michigan, Ann Arbor, MI*

STEVEN P. GELONE, PharmD • *Department of Pharmacy Practice, Temple University School of Pharmacy, Philadelphia, PA*

JANE M. GERVASIO, PharmD, BCNSP • *Methodist Hospital at Clarian Health Partners, Indianapolis, IN*

JEANETTE M. HASSE, PhD, RD, FADA, CNSD • *Baylor Institute of Transplantation Sciences, Baylor University Medical Center, Dallas, TX*

KATHLEEN L. HOOVER, MEd, IBCLC • *Department of Public Health, Maternal, Child and Family Health, Philadelphia, PA*
TANYA C. KNIGHT-KLIMAS, PharmD, CGP, FASCP • *Department of Pharmacy Practice, Temple University School of Pharmacy, Philadelphia, PA*
MICHAEL D. KRAFT, PharmD • *College of Pharmacy, University of Michigan and Department of Pharmacy Services, University of Michigan Hospitals and Health Centers, Ann Arbor, MI*
DEBORAH A. MAKA, PharmD • *Department of Pharmacy Services, The Children's Hospital of Philadelphia, Philadelphia, PA*
MARIANA MARKELL, MD • *Division of Renal Disease, State University of New York Health Science Center, Brooklyn, NY*
MARIA R. MASCARENHAS, MD • *Division of Gastroenterology and Nutrition, The Children's Hospital of Philadelphia, Philadelphia, PA*
JEFFREY J. MUCKSAVAGE, PharmD, BCPS • *College of Pharmacy, University of Illinois at Chicago, Chicago, IL*
JUDITH A. O'DONNELL, MD • *Department of Medicine, Drexel University College of Medicine and School of Public Health, MCP Hospital-Division of Infectious Diseases, Philadelphia, PA*
AMEETA PAREKH, PhD • *Office of Clinical Pharmacology and Biopharmaceutics, Center for Drug Evaluation and Research, U.S. Food and Drug Administration, Rockville, MD*
HONESTO M. POBLETE, JR., MD • *Department of Surgery, Drexel University College of Medicine, Philadelphia, PA*
ROBERT B. RAFFA, PhD • *Department of Pharmaceutical Sciences, Temple University School of Pharmacy, Philadelphia, PA*
CAROL J. ROLLINS, MS, RD, CNSD, PharmD, BCNSP • *University of Arizona College of Pharmacy and Nutrition Support Team, University Medical Center, Tucson, AZ*
FRANCIS E. ROSATO, JR., MD • *Department of Surgery, Thomas Jefferson University Hospital, Philadelphia, PA*
LESLIE SCHECHTER, PharmD • *Department of Pharmacy, Thomas Jefferson University Hospital, Philadelphia, PA*
YVETTE R. SCHLUSSEL, PhD • *Department of Nutritional Sciences, Rutgers, The State University, New Brunswick, NJ*
SUE A. SHAPSES, PhD, RD • *Department of Nutritional Sciences, Rutgers, The State University, New Brunswick, NJ*
MARCIA SILKROSKI, RD • *Nutrition Advantage, Chester Springs, PA*
BURGUNDA V. SWEET, PharmD • *Drug Information and Investigational Services, College of Pharmacy, University of Michigan Health System, Ann Arbor, MI*
RAYMOND C. TALUCCI, II, MD, FACS • *Department of Surgery, Drexel University College of Medicine, Hahnemann Hospital, Philadelphia, PA*
ALLISON WOOD WALLACE, PharmD, BCPS • *Duke University Medical Center, Durham, NC*
MATTHEW J. WEISS, MD • *Department of Surgery, Johns Hopkins Hospital, Baltimore, MD*
PATRICIA WORTHINGTON, RN, MSN, CNSN • *Department of Nursing, Thomas Jefferson University Hospital, Philadelphia, PA*
RONIT ZILBERBOIM, PhD • *Lonza Inc., Annandale, NJ*

Value-Added eBook/PDA

This book is accompanied by a value-added CD-ROM that contains an Adobe eBook version of the volume you have just purchased. This eBook can be viewed on your computer, and you can synchronize it to your PDA for viewing on your handheld device. The eBook enables you to view this volume on only one computer and PDA. Once the eBook is installed on your computer, you cannot download, install, or e-mail it to another computer; it resides solely with the computer to which it is installed. The license provided is for only one computer. The eBook can only be read using Adobe® Reader® 6.0 software, which is available free from Adobe Systems Incorporated at www.Adobe.com. You may also view the eBook on your PDA using the Adobe® PDA Reader® software that is also available free from Adobe.com.

You must follow a simple procedure when you install the eBook/PDA that will require you to connect to the Humana Press website in order to receive your license. Please read and follow the instructions below:

1. Download and install Adobe® Reader® 6.0 software
   You can obtain a free copy of Adobe® Reader® 6.0 software at www.adobe.com
   **Note: If you already have Adobe® Reader® 6.0 software, you do not need to reinstall it.*
2. Launch Adobe® Reader® 6.0 software
3. Install eBook: Insert your eBook CD into your CD-ROM drive
   PC: Click on the "Start" button, then click on "Run"
   At the prompt, type "d:\ebookinstall.pdf" and click "OK"
   **Note: If your CD-ROM drive letter is something other than d: change the above command accordingly.*
   MAC: Double click on the "eBook CD" that you will see mounted on your desktop. Double click "ebookinstall.pdf"
4. Adobe® Reader® 6.0 software will open and you will receive the message "This document is protected by Adobe DRM" Click "OK"
   **Note: If you have not already activated Adobe® Reader® 6.0 software, you will be prompted to do so. Simply follow the directions to activate and continue installation.*
   Your web browser will open and you will be taken to the Humana Press eBook registration page. Follow the instructions on that page to complete installation. You will need the serial number located on the sticker sealing the envelope containing the CD-ROM.

If you require assistance during the installation, or you would like more information regarding your eBook and PDA installation, please refer to the eBookManual.pdf located on your CD. If you need further assistance, contact Humana Press eBook Support by e-mail at ebooksupport@humanapr.com or by phone at 973-256-1699.