COMPREHENSIVE DERMATOLOGIC DRUG THERAPY

SECOND EDITION

STEPHEN E. WOLVERTON

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Preface

The second edition of *Comprehensive Dermatologic Drug Therapy* has been a labor of love, and has been surprisingly challenging for several reasons. I have attempted to maximize the inclusion of new information and formatting approaches, while likewise refining the prior content and special features of this book.

Counting the original book *Systemic Drugs for Skin Diseases* published in 1991, the process has included growth from 17 chapters to 50 chapters (first edition of the current title) and now 60 chapters in the second edition of the current title. Always focusing on various means of continued editorial improvement to assist the student/learner of Dermatologic Pharmacology, I will briefly relate how the second edition of *Comprehensive Dermatologic Drug Therapy* addresses three related questions: "What is new?", "What is improved?", and "What is the same?".

Again in this section, I thank a fantastic group of authors for sharing their knowledge and expertise, their clinical experience, and their creativity in producing this book … to the authors, thanks for a job well done! I trust that all of you will enjoy the product of your hard work and expertise.

WHAT IS NEW?

New chapters: The following chapters are either totally new topics or are derived from prior chapters divided* to expand topic coverage and emphasis:

Chapter 3 (Polymorphisms)
Chapter 18 (Photodynamic Therapy)
Chapter 19 (TNF Inhibitors)*
Chapter 20 (T-Cell Activation Inhibitors)*
Chapter 25 (Intravenous Immunoglobulin Therapy)
Chapter 27 (Drugs for the Skinternist)
Chapter 35 (Topical Contact Allergens)*
Chapter 36 (Topical Calcineurin Inhibitors)*
Chapter 45 (Systemic Adverse Effects Due To Topical Medications)
Chapter 46 (Compounding in Dermatology)
Chapter 48 (Botulinum Toxin Injections)
Chapter 52 (Drug-Induced Malignancy)
Chapter 59 (Pharmacovigilance)
Chapter 60 (Dermatologic Drug Therapy in Children)

Biologic agents in dermatologic therapeutics: Chapters 19 and 20 above, along with Appendix 1 seek to keep up with this rapidly evolving and exciting "new" area of Dermatologic Pharmacology.

New authors: A total of 36 new authors have contributed towards this book project.

Important questions: Almost 500 questions posed at the beginning of each chapter help to guide the reader towards specific text locations for answers to challenging areas of central importance to our field.

Drug mechanism figures: These include 11 detailed drug mechanism figures with comprehensive footnotes that I developed, supplemented by a substantial number of creative figures provided by the individual authors.

WHAT IS IMPROVED?

Drug interactions tables: These tables are derived from Facts & Comparisons, Epocrates, The Medical Letter of Drugs and Therapeutics, and Hansten and Horn's Top 100 Drug Interactions databases, formatted by (1) similar drug interaction types, and (2) keeping drugs grouped and compared by category.

The chapter references: These have been substantially updated, with a very high percentage from the year 2000 on.

More drug structures: There are now just over 100 total drug structures listed in over 40 figures allowing comparison for related drugs.

WHAT IS THE SAME?

Monitoring guidelines boxes: This tradition of the prominent "drug safety" theme throughout the book is continued and updated.

Indications and contraindications boxes: This theme is another tradition that is continued and yet updated and refined.

General philosophy: I continue to strive to assist authors in providing concise, practical, and relevant information in just over 1000 pages of text.

Emphasis on rapid retrieval of information: The continued emphasis on using numerous tables and boxes, coupled with formatting with multiple headings and subheadings are all of value in this priority for the busy clinician.

Stephen E. Wolverton MD

Dedication

This book is dedicated to the following individuals:

To my wife Cheryl ... for her support and help over the past 18 months of the book development and the editorial process, let alone our 26 years of marriage.

To our sons Jay Edward (age 20) and Justin David (age 18) ... now in the early part of their college years, for having a wonderfully diverse set of interests and for being a source of continuing joy over the past two decades.

To my parents Elizabeth Ann (1924–2000) and Dr. George M. Wolverton Sr. ... for the passion, wisdom, compassion and encouragement provided throughout their lives.

And to my wonderful (and large) nuclear family with three sisters (Anne, Cynthia, and Pam) and five brothers (George, Greg, Jeff, Doug, and Dan) ... for their kindness to and consideration for others, and their ongoing camaraderie throughout our lives.

Acknowledgements

I would like to sincerely thank and applaud the following individuals for their energetic and kind support of my journey through the book development and editorial process for the second edition of "Comprehensive Dermatologic Drug Therapy". I am indebted to all of you for your efforts.

From the UK (with Elsevier ties)

Martin Mellor (project development editor) for the initial "fortnightly", and eventually weekly, conference calls over the past year or so and plethora of e-mails to authors utilizing diplomatic assertiveness to keep chapters moving through first and second drafts, and on through page proof phase. Having done this process myself for my prior books, it has been a great relief having your help for these communication and motivational roles.

Bryan Potter (production manager) and Charles Lauder (copy editor) both possessing a remarkable attention to detail and having tremendous efficiency, from finding duplicated references, to insightful questions on content, to finding issues in different chapters not in initial agreement, to formatting the book in a easy to read fashion.

Karen Bowler, and her predecessor Sue Hodgson, (acquisitions editors) for the early book development and for coordinating the multiple departments involved with the book publication.

WB Saunders (the imprint of this book) and Elsevier for the broader role in oversight from the beginning of the book development through marketing the final product.

From the "States" (with Indiana University School of Medicine ties)

Megan Landis, currently a third year medical student at Indiana University, who focused on electronic information retrieval concerning the roughly 100 individual drug structures and the daunting task of background work for drug interactions, enabling me to collate a wealth of information from four different drug interaction databases.

Kelli Cassidy, our dermatology residency coordinator, who worked closely with Martin Mellor concerning author communications during the challenging first and second drafts phases of the book, for helping to maintain an active and accurate database of author information.

My colleagues from Indiana University—Drs. Jeff Travers, David Gerstein, Beth Brogan, Charles Lewis, and Gene Kim—who provided coverage for a significant number of my clinics enabling the 3- and 4-day weekends so critical for the book editing process.

Mary Heil and Amanda Young from our departmental administrative staff, for helping to copy and send to the publisher the page proofs.

Dr. Henry Besch Jr., emeritus Indiana University Pharmacology chair, who again helped with editing the drug structures for this book.

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Jen Reddan Pharm. D. and her staff with Clarian health partners associated with the Indiana University School of Medicine for their careful work with drug costs.

From the "States" and the World (the Authors)

The 90 authors for this book edition who responded very, very well to the task of updating prior chapters and creating totally new chapters. These authors responded in a superior fashion to the challenges I requested of them. In particular, I highlight the following individuals:

The authors who contributed to all three versions of my book (including the original title *Systemic Drugs from Skin Diseases*, 1991 edition): Brian Berman, Jeff Callen, Charles Camisa, Carol Culp-Shorten, Loree Davis, and Marshall Kapp.

The international cast of 13 authors from Canada, Europe and Southeast Asia: Robert Bissonnette, Malcolm Greaves, Aditya K. Gupta, Sandra Knowles, Andrew Lin, Thomas Luger, Christian Murray, Jaggi Rao, Anita Ruetter, Lori E. Shapiro, Neil Shear, Nowell Solish, Kai Thomas.

The authors who contributed to two or more chapters—Andrew Lin (three chapters), plus Jeff Callen, Charles Camisa, John Koo, Chai Sue Lee, Ben Lockshin, and Neil Shear who contributed two chapters each.

And the first time authors—36 total—including a number of clinicians and educators who provided fresh ideas for established chapters from the prior book edition.

A Dozen Suggestions to Help the Reader Optimally Utilize This Book

- If you want general concepts and references concerning **drug use** for a **specific dermatologic condition** then there are three related solutions in this book. The Indications and Contraindications boxes, the well-formatted, easy to locate pertinent text sections, and the grouping of references by topic will guide your way for information to treat specific patients.
- If you want to **retrieve information** or learn about the complicated subject of **drug interactions** then the Drug Interactions tables will assist in both tasks. The 33 Drug Interactions tables are expanded substantially from the previous edition to summarize four distinct respected databases, formatted for efficient information retrieval and to facilitate understanding general concepts of drug interactions.
- If you want to **prepare** for pharmacology and therapeutics components of the **Dermatology Board Examination** or **Recertification Examination** (let alone efficiently gain a general understanding of drugs in dermatology) then the important questions at the beginning of each chapter will assist you in all these goals. The answers for each question are easily found in the text, referenced by page number and marked with a distinctive icon.
- If you want to gain a general **understanding** concerning **how drugs work** then all chapters discussing specific drugs have Mechanism of Action sections. These sections focus on the mechanisms for a drug's therapeutic benefits and potential adverse effects, with many summarized in table format. In addition, more in-depth knowledge concerning drug mechanisms can be derived from carefully footnoted and highlighted Drug Mechanism figures.
- If you want drug **pharmacology concepts** and **product information** in a "nutshell" then there are tables for drugs discussed in the chapter and Key Pharmacology Concepts for most systemic drugs and many topical therapies as well.
- If you want to **maximize** systemic **drug safety** with appropriate **monitoring** of laboratory tests, related tests or special examinations for a given drug then the Monitoring Guidelines boxes continue to demonstrate an appropriate standard of care for early detection of the various drugs' most important potential adverse effects.
- If you want to gain a broad **understanding** of a given drug or drug group's **adverse effects** then each chapter has an Adverse Effects section for each major drug discussed. A substantial number of chapters have an Adverse Effects box summarizing, grouping, and prioritizing important potential drug risks, plus 6 of the book's chapters (Chapters 50 through 55) focus specifically on important potential adverse effects.
- If you want to **learn** more about **systemic drug costs** then Appendix 3 (Selected Drugs Costs) and the "Price Index" in a substantial number of chapters will assist you. In Appendix 3, current average wholesale prices can be compared with average wholesale prices from 5–6 years ago and current retail prices as well.
- If you want a general **understanding** of **drug structures**, particularly in comparing different drugs in the same class then there are just over 100 drug structures throughout book to assist your visual understanding of these drugs.
- If you want concise information concerning **drugs released** during the book editorial process, **drugs pending approval** in the near future, or for new uses of older drugs recently gaining momentum in dermatology then Appendix 1 (Biologics on the Horizon and Newer Uses of Older Biologics) and Appendix 2 (Some Additional "New" Drugs) supplement attempts throughout the book to be maximally current with important drug information.
- If you would like to **read supplemental information** on a given **drug** or **drug group**, or a related topic in pharmacology then the Bibliography: Important Reviews and Chapters following the text for each chapter lists about 6–8 relatively recent reviews, chapters and books on the various topics under the chapter title, usually grouped under headings to allow easy selection.
- Or, if you just want to **learn or relearn** any topic covered in *Comprehensive Dermatologic Drug Therapy* in a complete yet efficient fashion, then the well-formatted chapters with a substantial number of tables, boxes, and figures will maximize the learning or relearning process. Just be sure to enjoy the process on this very interesting educational journey!

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Part I

Introduction

Chapter 1

Basic Principles of Pharmacology

Stephen E. Wolverton

Q1-1 What are the simplest definitions of "pharmacokinetics" and "pharmacodynamics"? **(Pg. 3, Table 1-1)**

Q1-2 What are several drugs or drug families for which the absorption may be altered by (a) cations such as iron, calcium, and magnesium, and (b) gastric pH? **(Pg. 4)**

Q1-3 What are several examples in which sustained exposure to a drug may give reduced positive or negative pharmacologic effects at the drug receptor level? **(Pg. 7, Table 1-4)**

Q1-4 What are several of the most important agonists and antagonists at the level of specific receptors? **(Pg. 8, Table 1-5)**

Q1-5 What are several of the most important examples in which drugs inhibit specific enzymes? **(Pg. 8, Table 1-6)**

Q1-6 What are several of the most important examples of prodrug and active drug relationships? **(Pg. 11, Table 1-8)**

Q1-7 Pertaining to drug excretion, (a) what are three important routes of drug excretion, and (b) what is the overall general change in the active drug that makes excretion possible? **(Pg. 11)**

Q1-8 What are the most important drug and cutaneous properties that allow for significant percutaneous absorption? **(Pg. 12)**

INTRODUCTION

This chapter is a relatively brief overview of basic principles of pharmacology, intended as a primer to maximize understanding of the remaining chapters of the book. There is by design some overlap with other chapters in the book, in order to address relevant issues from a number of vantage points. Of particular relevance to this chapter are the following: Chapter 2, Principles for Maximizing the Safety of Dermatologic Drug Therapy; Chapter 50, Hepatotoxicity of Dermatologic Drug Therapy (contains detailed information on hepatic metabolism of drugs); and Chapter 54, Drug Interactions. The reader is encouraged to pursue further detailed information and references (cited in the respective chapter for specific drugs) for drug examples used to illustrate basic principles of pharmacology in this chapter. A bibliography format alone on pharmacologic general principles is utilized for this chapter.

The primary focus of the chapter will be on pharmacologic principles related to systemic drugs. A relatively brief section on Percutaneous Absorption will conclude the chapter. The basic goal of this chapter (and for the rest of the book as well) is to describe and illustrate pharmacologic principles that will enable the clinician to maximize the efficacy and to minimize the risk (adverse effects, drug interactions) of dermatologic drug therapy. It is my hope that this chapter will provide a broad foundation for true understanding of pharmacology to enable clinicians to achieve:

(1) More efficient assimilation of new information on medications,
(2) Adaptability to the many unpredictable responses of patients to medications, and
(3) Better long-term retention of important information on all aspects of drug therapy.

Outline for the Chapter

Q1-1 Traditionally, discussions on basic pharmacology divide the topic into two domains (Table 1-1): pharmacokinetics (what the body does to the drug) and pharmacodynamics (what the drug does to the body). As a relatively novel way of presenting this information, I will discuss topics in sequence as seen through the "eyes" of the drug as it progresses

Table 1-1: Two "Entry Level" Definitions

Term	Definition
Pharmacokinetics	What the *body does to* the *drug*—from entry into the body until excretion of the drug or its metabolites
Pharmacodynamics	What the *drug does to* the *body*—once at site of action; from receptor binding through the definitive effect (desired or adverse)

Table 1-2: Pharmacokinetics—Major Components*

Component	Most important issues
Absorption	Relatively lipophilic drugs are more optimally absorbed through the GI tract; lipophilic or hydrophilic drugs relatively equal for parenteral absorption
Distribution	Body compartments to which the drug is dispersed; important subcomponents include fatty tissues and blood–brain barrier
Bioavailability	Percentage of administered drug reaching circulation; also relates to free (active) versus protein-bound drug
Metabolism	Lipophilic drugs are converted to more hydrophilic metabolites to enable excretion
Excretion	The above conversion to hydrophilic metabolites allows renal or biliary excretion; other synonyms—clearance, elimination

*These components as related to oral (enteral) or parenteral administered drugs

through the human body. In broad strokes, the sequence will be:

(1) Pharmacokinetics (part I—absorption, distribution, bioavailability): the drug must enter the body, travel to, and be "available" at the site of desired pharmacologic action;
(2) Pharmacodynamics: the drug interacts with a receptor/effector mechanism, producing both desirable and undesirable effects; and
(3) Pharmacokinetics (part II—metabolism, excretion): the drug and/or its metabolites must leave the body.

Each of the above steps has a number of variables (with both predictable and unpredictable components) for which the clinician should have at least a baseline working knowledge. These variables will be presented and illustrated under each chapter heading that follows.

PHARMACOKINETICS—PART I (TABLES 1-2 AND 1-3)

Drug Absorption (The drug has to enter the body.)

The routes of drug administration most pertinent to dermatology in order of descending frequency of use are topical, oral, intramuscular, and intralesional administration. Intravenous drug administration is uncommonly ordered by the dermatologist. Typically, drugs must be relatively lipophilic (nonionized, nonpolar) to "enter" the body by topical or oral routes; whereas, relatively hydrophilic (ionized, polar) drugs can still "enter" by intramuscular and intravenous routes. Upon absorption, drugs still must traverse other cell membranes in order to reach the intended destination(s). Again, a drug with lipophilic qualities is rewarded by the ability to traverse these lipid bilayers to arrive at the site of desired pharmacologic action.

Several other variables may affect the absorption of drugs by oral administration. Q1-2 Certain drugs are absorbed less efficiently in the presence of food. In descending order the impact of food on tetracycline family drug absorption is as follows: tetracycline > doxycycline > minocycline. Divalent and trivalent cations in milk (calcium), various traditional antacids (aluminum-, magnesium-, calcium-containing), and iron-containing products can reduce the absorption of the above tetracyclines, as well as fluoroquinolone antibiotics. Gastric pH is yet another variable that influences drug absorption. An example would be the necessity for a relatively low gastric pH for ketoconazole and itraconazole to be optimally absorbed, whereas the gastric pH is not a critical determinant for fluconazole absorption. The above absorption variables are the basis for a number on drug interactions that do not involve the cytochrome P-450 (CYP) system.

A few other points are worth considering under this heading. Some drugs have negligible absorption with oral administration, yet can have a pharmacologic value in the GI tract. Several examples would be the use of oral cromolyn sodium (Gastrochrome) for the GI manifestations of mastocytosis, as well as the use of nystatin for reduction of bowel Candida