Charles D. Ciccone

Pharmacology in Rehabilitation

FIFTH EDITION

Contemporary Perspectives in Rehabilitation

POTENTIAL INTERACTIONS BETWEEN PHYSICAL AGENTS AND THERAPEUTIC DRUGS

Listed here are some potential interactions between physical agents used in rehabilitation and various pharmacological agents. It is impossible to list all the possible relationships between the vast array of therapeutic drugs and the interventions used in physical therapy and occupational therapy. However, some of the more common interactions are identified here.

Modality	Desired Therapeutic Effect	Drugs With Complementary/ Synergistic Effects	Drugs With Antagonistic Effects	Other Drug-Modality Interactions
Cryotherapy				
Cold/ice packs Ice massage Cold bath Vapocoolant sprays	Decreased pain, edema, and inflammation	Anti-inflammatory steroids (glucocorticoids); nonsteroidal anti-inflammatory analgesics (aspirin and similar NSAIDs)	Peripheral vasodilators may exacerbate acute local edema.	Some forms of cryotherapy may produce local vasoconstriction that temporarily impedes diffusion of drugs to the site of inflammation.
	Muscle relaxation and decreased spasticity	Skeletal muscle relaxants	Nonselective cholinergic agonists may stimulate the neuromuscular junction.	—
Superficial and Deep Heat				
Local application Hot packs Paraffin Infrared Fluidotherapy Diathermy Ultrasound	Decreased muscle/ joint pain and stiffness	NSAIDs; opioid analgesics; local anesthetics	—	—
	Decreased muscle spasms	Skeletal muscle relaxants	Nonselective cholinergic agonists may stimulate the neuromuscular junction.	—
	Increased blood flow to improve tissue healing	Peripheral vasodilators	Systemic vasoconstrictors (e.g., alpha-1 agonists) may decrease perfusion of peripheral tissues.	—
Systemic Heat				
Large whirlpool Hubbard tank	Decreased muscle/joint stiffness in large areas of the body	Opioid and nonopioid analgesics; skeletal muscle relaxants	—	Severe hypotension may occur if systemic hot whirlpool is administered to patients taking peripheral vasodilators and some antihypertensive drugs (e.g., alpha-1 antagonists, nitrates, direct-acting vasodilators, calcium channel blockers).
Ultraviolet Radiation	Increased wound healing	Various systemic and topical antibiotics	—	Antibacterial drugs generally increase cutaneous sensitivity to ultraviolet light (i.e., photosensitivity).
	Management of skin disorders (acne, rashes)	Systemic and topical antibiotics and anti-inflammatory steroids (glucocorticoids)	Many drugs may cause hypersensitivity reactions that result in skin rashes, itching.	Photosensitivity with antibacterial drugs
Transcutaneous Electrical Nerve Stimulation (TENS)	Decreased pain	Opioid and nonopioid analgesics; certain antiseizure drugs (e.g., gabapentin, pregabalin)	Opioid antagonists (naloxone, naltrexone)	—
Functional Neuromuscular Electrical Stimulation	Increased skeletal muscle strength and endurance	Low-dose androgens in certain populations (e.g., androgen-deficient men)	Skeletal muscle relaxants	—
	Decreased spasticity and muscle spasms	Skeletal muscle relaxants	Nonselective cholinergic agonists may stimulate the neuromuscular junction.	—

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Contemporary Perspectives in Rehabilitation

Steven L. Wolf, PT, PhD, FAPTA, Editor-in-Chief

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FIFTH EDITION

F.A. Davis Company • Philadelphia

F. A. Davis Company
1915 Arch Street
Philadelphia, PA 19103
www.fadavis.com

Printed in the United States of America

Last digit indicates print number: 10 9 8 7 6 5 4 3 2 1

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Library of Congress Cataloging-in-Publication Data

Ciccone, Charles D., 1953- , author.
Pharmacology in rehabilitation / Charles D. Ciccone. — Fifth edition.
p. ; cm.
Includes bibliographical references and index.
ISBN 978-0-8036-4029-0 — ISBN 0-8036-4029-3
I. Title.
[DNLM: 1. Drug Therapy. 2. Pharmacokinetics. 3. Pharmacological Phenomena. 4. Rehabilitation. WB 330]
RM301
615'.1—dc23

2015003583

Dedicated to Penny, Kate, Alex, and Rosemary.
I continue to be inspired by your faith and support throughout the years.

Foreword to the Fourth Edition

There are very peculiar ways in which one can mark time. We often do so by observing the rate at which our siblings, children, or grandchildren grow, especially when we are not in daily contact, or by how we inevitably underestimate the length of time transpired since we last encountered an old friend. In this context, it seems remarkable that over 13 years have transpired since I first discussed with Chuck Ciccone the prospects for a text on pharmacology for our *Contemporary Perspectives in Rehabilitation*. The realization that the first edition of *Pharmacology in Rehabilitation* appeared more than a decade ago is even more astounding. The basis for the genesis of such a book was founded on the belief that rehabilitation specialists received little formal training about drug interactions and how any single pharmacological agent could impact either treatment plans or outcomes. Chuck took it upon himself to generate a text that would address this educational and clinical shortcoming. The result is very clear. *Pharmacology in Rehabilitation* is the "gold standard" among all texts addressing this content for nonphysician rehabilitation specialists.

So why is it important to create a fourth edition within one decade? Why is a more superficial compendium of information about drugs and their actions inadequate? The answer to these questions is directly related to the rapidly emerging responsibilities incumbent upon rehabilitation specialists. During the past 5 years, the advent of clinical doctoral programs in physical and occupational therapy has heralded a rapid transformation in these educational arenas. Several attributes now take on a meaning that previously might have been underappreciated. First, the label of "doctor" implies an ***expectation*** on the part of the consumer that the practitioner is the penultimate expert on providing an analysis and treatment plan for improving upon the pathology of any system's movement, whether muscle, joint, pulmonary, etc. Second, given the status associated with the professional label, there is an associated ***obligation*** on the part of the practitioner to address all aspects of the patients' signs and symptoms. This obligation requires that the clinician differentiate patient responses to treatment from patient responses to pharmacy. As one physical therapist so astutely told me, her recognition that a patient was not responding to pain medication taken well above the specified dosage, in the absence of any evidence for malingering behavior, resulted in the subsequent detection and successful removal of a renal tumor. Third, as practitioners, the DPT or DOT now assumes a greater ***responsibility*** for keeping a contemporary knowledge base about the interface between treatment plan and concurrent synergies or exacerbations that might result from single or multiple medications taken by the patient.

This collection of attributes can be best appreciated if the student is first informed and the clinician

is educated about the most recent medications, their pharmokinetics, and the interactions they have with patients with specific diagnoses. Since the drug industry is arguably one of the most dynamic corporate structures in the world, changes in pharmacy occur at an alarmingly fast rate, one that will increase even more dramatically as transplants and the sequelae resulting from genetic engineering (as two examples) take on greater roles in medicine. Such rapid changes, then, call for contemporary and comprehensive updates in available information. Such updates must be presented in a manner that is compelling, yet easy to understand.

Inclusive in this perception is the absolute requirement that the student or clinician be able to relate to the text meaningfully. Toward this important goal, the 4th edition of *Pharmacology in Rehabilitation* is designed to address rehabilitation relevance in every clinical chapter as well as to present important case histories to reinforce this relevance. New materials on agents used in or even as complementary and alternative medicines have been added. Moreover, we have made efforts to add to the appeal of the book through the addition of colorization, use of double columns, and encasing the text within a newly designed hard cover. These changes are in contradistinction to one standard that remains immutable—Dr. Ciccone's remarkable gift for taking complex material and making it easy to understand.

For those clinicians who have in their possession early editions of this book, I invite you to compare your copy to the 4th edition as validation for the assertions made in this Foreword. We have not compromised the comprehensive nature of this volume in favor of a "simpler" approach to understanding pharmacology. We believe that the topic, by its very nature and from the implications inherent in its knowledge base, requires a comprehensive, yet user-friendly, delivery. This belief system remains unhindered in this latest edition; yet the problem-solving and evidence-based nature of the content is preserved and enhanced.

The thought of having a reference text for rehabilitation specialists was considered by us to be a unique concept 13 years ago. Today, many doctoral programs include pharmacology as a separate course or as an important component in teaching the rationale for treatment approaches and their assessment. There is much gratification to be gained from recognizing this transformation and in knowing that the content of this book contributes to the evolving maturation of our educational programs and our clinical services.

Steven L. Wolf, PT, PhD, FAPTA
Series Editor

Preface

As in the past, I was excited, albeit somewhat apprehensive, to start working on a new edition of this book. I always joke that I should have written a text on gross anatomy—human structures have not changed much in the few years since the last edition. Pharmacology, however, continues to change and expand as new drugs are developed and we explore how patients respond to various drug regimens. Pharmacology has likewise taken advantage of scientific developments in other areas to enhance patient outcomes. For example, the Human Genome Project, nanotechnology, and creation of monoclonal antibodies were still in their infancy when I began working on the first edition of this text. These and other scientific breakthroughs are now an important part of drug development, and they continue to contribute to innovative and clinically relevant advances in pharmacotherapy.

Given all the advancements in pharmacology, I tried to maintain the basic ideas presented in previous editions—that is, I describe drug therapy from the perspective of how specific drugs work and how they can provide beneficial effects as well as adverse effects in patients undergoing physical rehabilitation. As in previous editions, I relied heavily on the peer-reviewed literature to provide current information, while trying to distill the wealth of information to the issues that are most relevant to our patients.

This edition starts with several chapters that address basic pharmacological principles, followed by chapters that deal with drugs used to treat specific disorders or achieve certain clinical outcomes. The text, figures, and tables were all updated, and new figures were added to several chapters to illustrate drug actions and effects. Case studies appear at the end of chapters that deal with specific clinical disorders. I revised all the case studies and changed the format so that several questions are posed within the case. Answers to these questions appear in an appendix at the end of the book. This change will hopefully engage readers and encourage application of information gleaned from the respective chapters.

Finally, I always appreciate the opportunity to write a new edition of this book. Pharmacology has certainly become an integral part of contemporary health care, and we must have a working knowledge of how drugs affect our patients. I hope that I have provided students and clinicians with a useful resource on this topic and that this text will ultimately help guide your practice when treating patients in a rehabilitation setting.

Charles D. Ciccone

Acknowledgments

I am grateful to all of the people who provided input and support as this book evolved through five editions. I must once again thank Barbara MacDermott Costa, Linda D. Crane, John F. Decker, Susan S. Glenney, Gary Gorniak, Mark Greve, Helen Wruble Hakim, Sandra B. Levine, Donald L. Merrill, Grace Minerbo, Peter Panus, Jeffrey Rothman, and Steven R. Tippett. Their expert advice when reviewing previous editions of this book has proven invaluable in laying the foundation for the current edition.

As always, the staff at F. A. Davis Company has been incredibly supportive in the development of this edition. I would like to especially thank Melissa Duffield, senior acquisitions editor, for her advice and encouragement while I was working on this project. Thanks also to production manager, Bob Butler; director of art and design, Carolyn O'Brien; and everyone else at F.A. Davis who helped bring this book to completion. I am likewise extremely grateful to Dean DeChambeau, who was the developmental editor on this project. Dean's suggestions, ideas, and careful attention to detail will undoubtedly make this a stronger and more clinically relevant text.

Finally, Steve Wolf has served as editor of the CPR series since its inception, and I remain indebted to him for his wisdom and support over the years. Likewise, all the students and clinicians I have worked with have unknowingly contributed to this book by asking good questions and reminding me how drug therapy is related to clinical practice. Their dedication to clinical practice is outstanding, and I hope I can repay their efforts with a book that is interesting, useful, and relevant.

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SECTION

1

General Principles of Pharmacology

CHAPTER 1

Basic Principles of Pharmacology

Pharmacology is the study of drugs. In its broadest definition, a drug can be described as "any substance that, when taken into a living organism, may modify one or more of its functions."[1] In this sense, a drug includes any substance that alters physiological function in the organism, regardless of whether the effect is beneficial or harmful. In terms of clinical pharmacology, it has traditionally been the beneficial or therapeutic effects that have been of special interest.

For centuries, people have used naturally occurring chemicals to relieve pain or treat disease. Almost everyone, for example, has been administered some form of natural product or home remedy that was handed down from generation to generation when trying to resolve a minor illness or painful condition. However, these natural cures and home remedies are understandably limited in how well they can treat more serious conditions. Within the past 100 years, medical practitioners have therefore expanded their use of natural, semisynthetic, and synthetic chemical agents to the point where many diseases can be prevented or cured, and the general health and well-being of many individuals has dramatically improved through therapeutic drug use. Current medical practitioners who prescribe and administer drugs (i.e., physicians and nurses) are expected to know the drugs and the basic mechanisms of their actions. It is now recognized that members of other health-related professions must have a fundamental knowledge of pharmacology as well.

RELEVANCE OF PHARMACOLOGY IN REHABILITATION

As a physical therapist, occupational therapist, or other rehabilitation specialist, you can expect that your patient will be using therapeutic medications. When you know how the various drugs may affect a patient and the mechanisms behind those effects, you can apply that knowledge to get an optimal response from the patient's therapy treatment. For instance, you can improve a patient's therapy session dramatically by scheduling the therapy when certain drugs reach their peak effect, such as drugs that decrease pain (analgesics) or improve the patient's motor skills (anti-Parkinson drugs). Conversely, some therapy sessions that require the patient's active participation can be rendered useless if scheduled when medications such as sedatives reach their peak effect. Also, when you understand a drug's pharmacological aspects, you can avoid or control any adverse responses from occurring due to direct interaction between the therapy treatment and certain medications. For example, a patient who is taking a peripheral vasodilator may experience a profound decrease in blood pressure in a hot whirlpool. By understanding the implications of such an interaction, you can be especially alert for any detrimental effects on the patient, or you may institute a different therapy treatment for them.

Pharmacology is a broad topic, so it is often subdivided into several areas of interest to help describe the discipline (Fig. 1-1). **Pharmacotherapeutics**

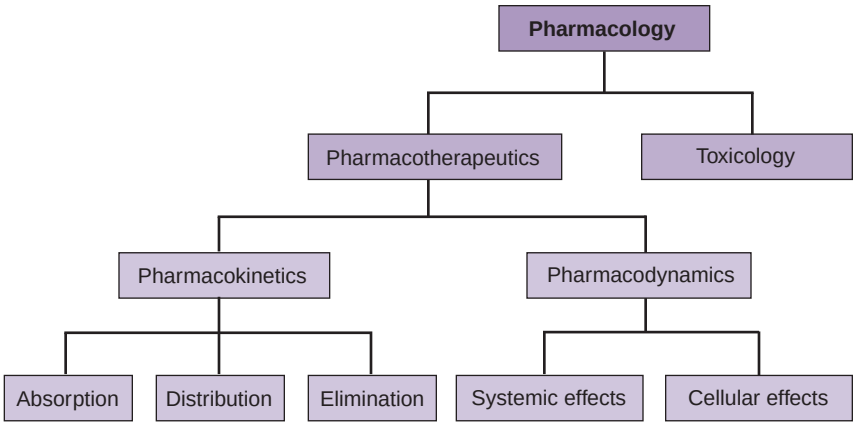

Figure ■ 1-1
Areas of study within pharmacology.

is the area of pharmacology that refers to the use of specific drugs to prevent, treat, or diagnose a disease. This text's primary concern is of the effects of drugs on humans, with animal pharmacology mentioned only in reference to drug testing and research in animals.

If we are to use therapeutic drugs safely, it is crucial to know how the body interacts with the drug and what effect it has on an individual. Consequently, pharmacotherapeutics is divided into two functional areas: pharmacokinetics and pharmacodynamics (see Fig. 1-1). **Pharmacokinetics** is the study of how the body absorbs, distributes, and eliminates the drug. **Pharmacodynamics** is the analysis of what the drug does to the body, including the mechanism by which the drug exerts its effect. Chapters 2 and 3 outline the basic principles of pharmacokinetics, and the pharmacodynamics and pharmacokinetics of specific drugs will be discussed in their respective chapters.

Toxicology is the study of the harmful effects of chemicals. Although it can be viewed as a subdivision of pharmacology, toxicology has evolved into a separate area of study. Toxicology is therefore considered a distinct discipline because of the scope of all the therapeutic agents' adverse effects, environmental toxins, and poisons. However, because virtually every medication can produce adverse effects, a discussion of toxicology must be included in pharmacotherapeutics. This text limits the discussions of drug toxicity to the unwanted effects that occur when therapeutic drugs reach excessively high (toxic) levels. The toxic side effects of individual drugs are covered in the chapters describing the therapeutic effects of that drug.

Pharmacy deals with the preparation and dispensing of medications. Although pharmacy is also frequently considered a subdivision of pharmacology, this area has evolved into a distinct professional discipline. The terms *pharmacy* and *pharmacology* refer to different areas of study and should not be used interchangeably.

Pharmacogenetics is a relatively new area of pharmacology.[2] It deals with the genetic basis for drug responses, especially variations in drug response from person to person. We know that individual differences in specific genes can alter pharmacokinetic and pharmacodynamic variables. These differences provide one reason why various people might react differently to the same drug. Examining the genetic code for a given patient could help predict which drugs might be most effective for that patient and which drugs should be avoided because of potentially harmful side effects. This process could help eliminate some of the trial and error that occurs when trying to find the best drug for that patient. Pharmacogenetics promises to play an increasing role in determining how drugs can be used safely and effectively.

Pharmacology is therefore an important aspect of health care that has direct relevance to patients in a rehabilitation setting. This chapter provides an overview of how drugs are named, classified, developed, and approved, and it will introduce concepts that help us compare the safety and effects of various drugs. Subsequent chapters will draw on this information when considering the effects of specific drugs on our patients.

DRUG NOMENCLATURE

One of the most potentially confusing aspects of pharmacology is the variety of names given to different drugs or even to the same compound. Students of pharmacology, as well as clinicians, are often faced

with myriad terms representing the same drug.[3,4] Many problems in drug terminology arise from the fact that each drug can be identified according to its *chemical*, *generic*, or *trade* name (Table 1-1).[4] **Chemical names** refer to the specific compound's structure and are usually fairly long and cumbersome. The **generic name** (also known as the *official* or **nonproprietary name**) tends to be somewhat shorter and is often derived from the chemical name. A **trade name** (also known as the *brand name*) is assigned to the compound by the pharmaceutical company and may or may not bear any reference to the chemical and generic terminology. An additional problem with trade names is that several manufacturers may be marketing the same compound under different names, adding to the confusion. Different drug companies may market the same drug if there is no existing patent for that compound or if the patent has expired.[5] For practical purposes, the generic name is often the easiest and most effective way to refer to a drug, and we will use this terminology frequently in this text.

Drug nomenclature is also a source of confusion and potential errors when different drugs have names that look or sound alike.[6] Practitioners could accidentally select and prescribe the wrong drug if its name sounds or looks like a different drug. This fact seems especially true for drugs with similar brand names.[7] Consider, for example, the confusion that could occur when trying to differentiate between the following three brand-name products: Celebrex, Cerebyx, and Celexa.[8] These three brand names correspond to an analgesic (see Chapter 15), an antiseizure drug (see Chapter 9), and an antidepressant (see Chapter 7), respectively. Despite their similar brand names, these three products represent three distinct pharmacological classes that are used in very different clinical situations. Hence, practitioners need to be especially careful when documenting the use of specific medications and make sure that the correct drug name is used to identify each product. In addition, patients are often concerned that a generic drug may represent a different and less effective product than its trade (brand) name counterpart. We address the issue of substituting generic products in the next section.

SUBSTITUTION OF GENERIC DRUGS FOR BRAND-NAME PRODUCTS

A common question among practitioners and patients is whether the generic form of a drug can be substituted for the brand-name product. The **generic drug** is typically less expensive than its brand-name counterparts, and substitution of a generic drug can help reduce health-care costs.[9] The generic form of the drug should be as safe and effective as the original brand-name product, provided that the generic form satisfies certain criteria.[10,11] Specifically, the generic form should undergo testing to establish that it has the same type and amount of the active ingredient(s), the same administration route, the same pharmacokinetic profile (e.g., drug absorption plasma levels, metabolism), and the same therapeutic effects as the brand-name drug.[12] If such testing is done, the two drugs are said to be "bioequivalent."[12]

Unless bioequivalence is established, however, it can only be assumed that substituting a generic drug will produce therapeutic effects that are similar to the brand-name drug. Likewise, establishing bioequivalence of a generic form does not guarantee that a given patient will not experience different effects from the generic form compared with the brand-name product. Some patients might simply respond differently to the generic form of a drug because of differences in their ability to absorb and metabolize certain generic

Table 1-1
EXAMPLES OF DRUG NOMENCLATURE

Chemical	Generic (Nonproprietary)	Trade/Brand-Name (Proprietary)
N-acetyl-*p*-aminophenol	Acetaminophen	Tylenol, Panadol, many others
3,4-Dihydroxyphenyl-L-alanine	Levodopa	Larodopa
5,5-Phenylethylbarbituric acid	Phenobarbital	Luminal, Eskabarb
7-Chloro-1,3-dihydro-1-methyl-5-phenyl-2*H*-1,4-benzodiazepin-2-one	Diazepam	Valium