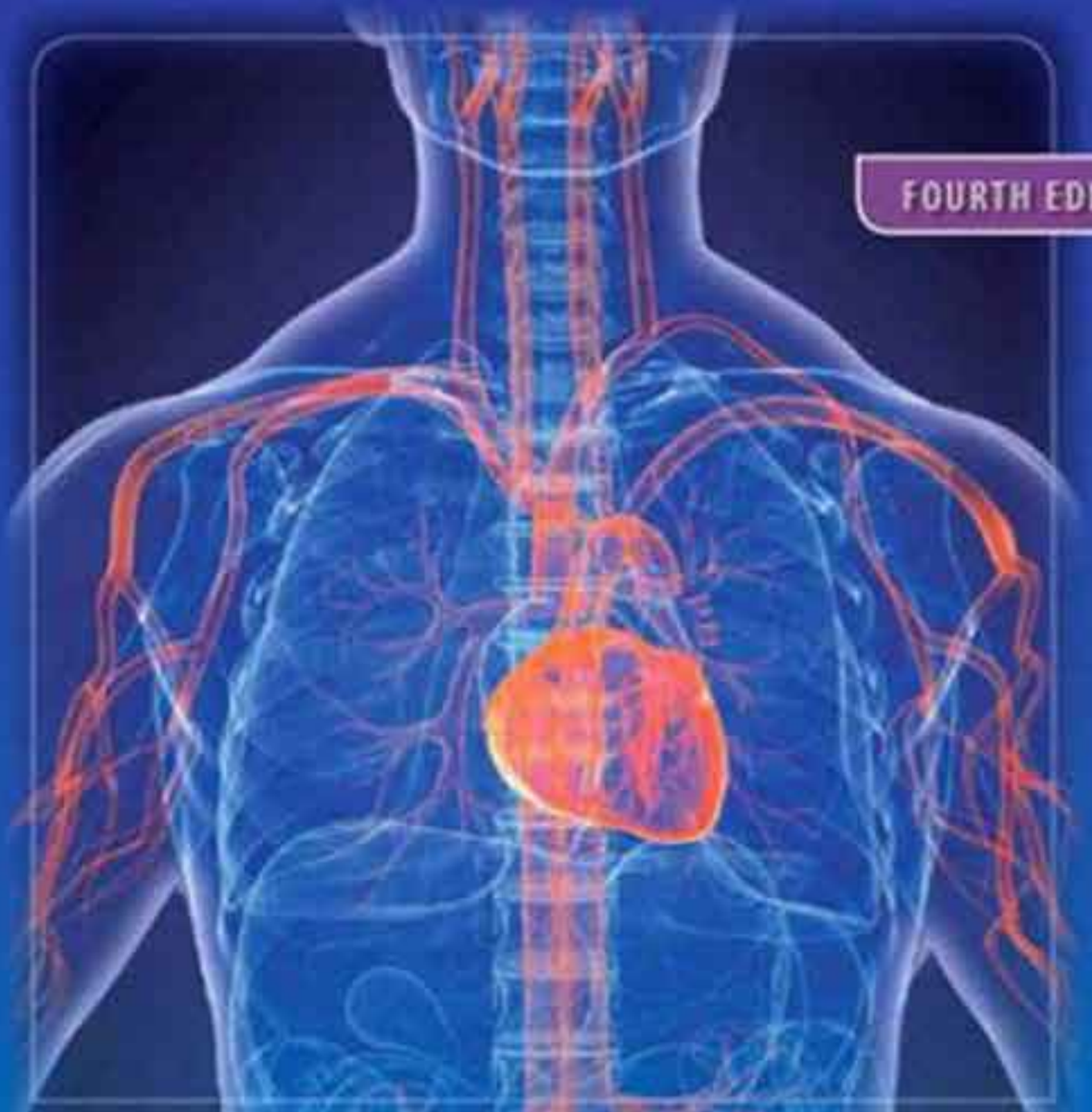
PHARMACOLOGY FOR NURSES

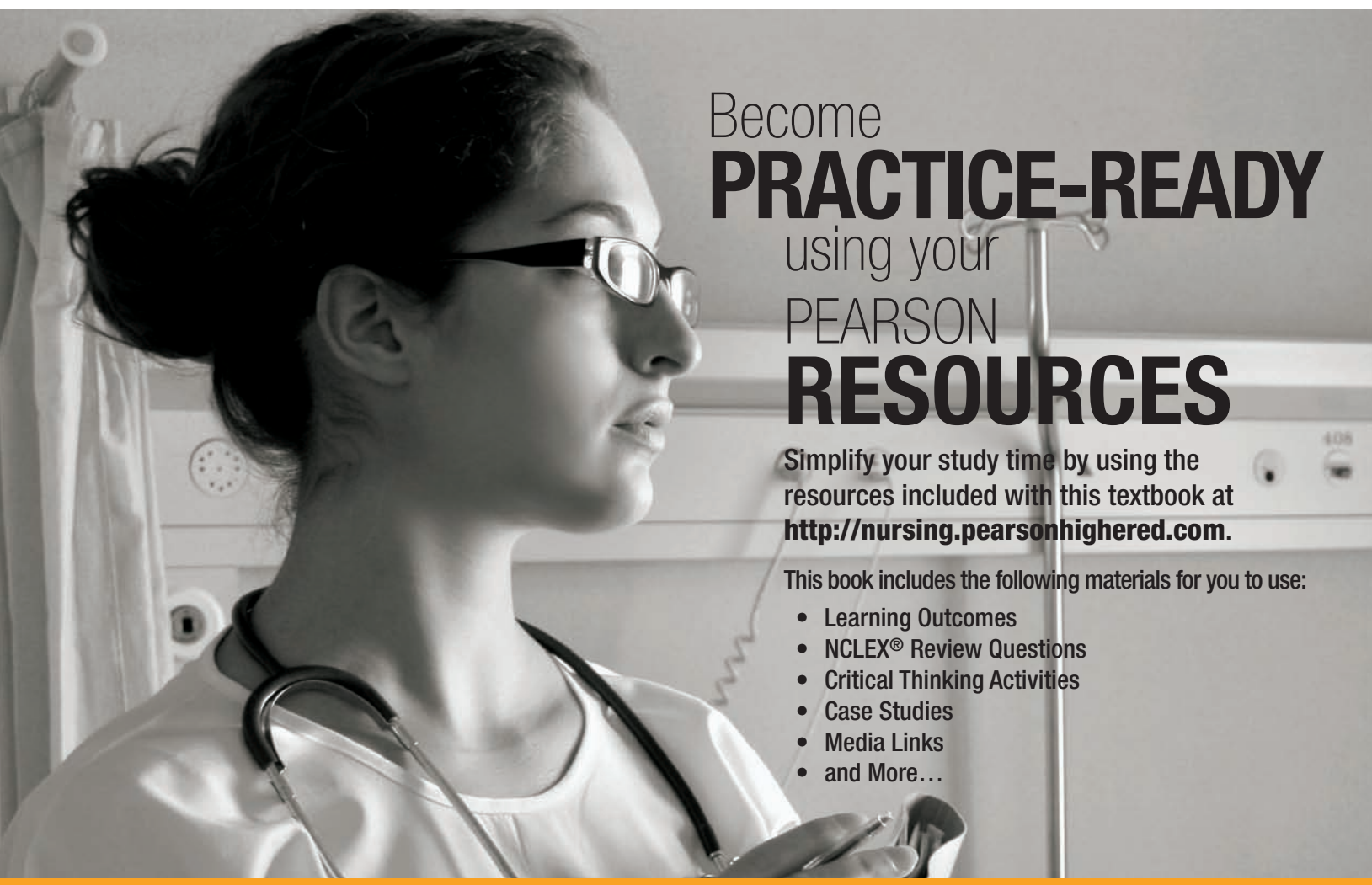
A Pathophysiologic Approach

FOURTH EDITION



MICHAEL ADAMS • NORMAN HOLLAND • CAROL URBAN

Brief Contents



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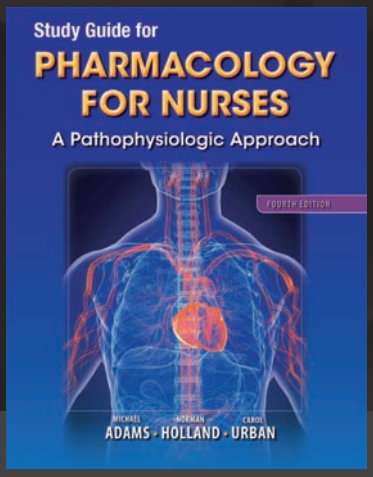

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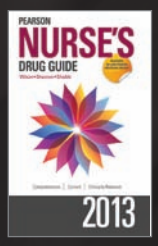

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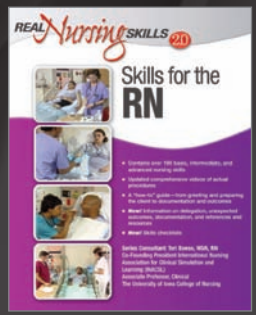

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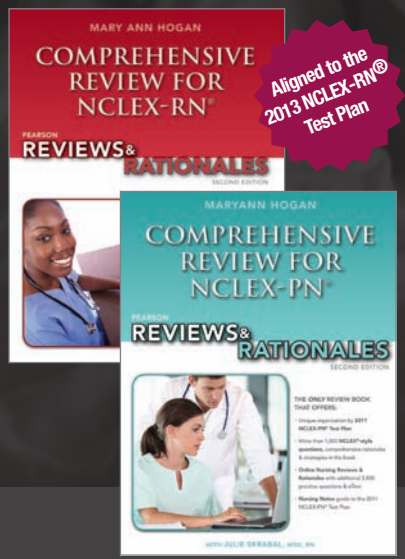

ALWAYS LEARNING

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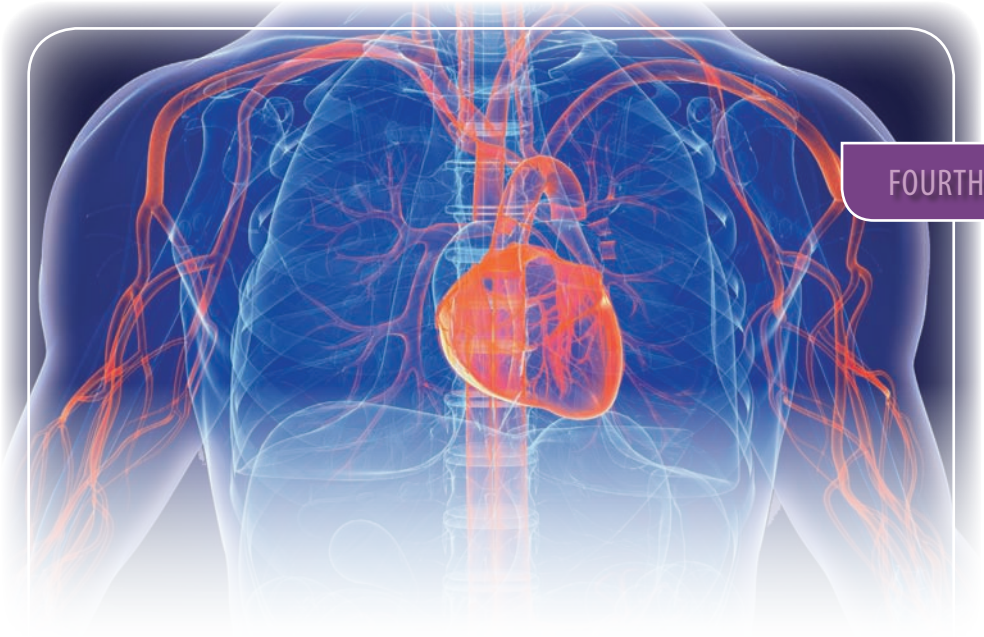
PHARMACOLOGY FOR NURSES

A Pathophysiologic Approach



FOURTH EDITION

Michael Patrick Adams
Professor of Anatomy and Physiology
St. Petersburg College
Formerly Dean of Health Professions
Pasco-Hernando Community College

Leland Norman Holland, Jr.
Program Manager
Hillsborough Community College
SouthShore Campus and
Professor of Pharmacology, MSN Nursing Program
Liberty University

Carol Quam Urban
Assistant Dean for Undergraduate Nursing
Assistant Professor, George Mason University
School of Nursing

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The authors and publisher have exerted every effort to ensure that drug selections and dosages set forth in this text are in accord with current recommendations and practice at the time of publication. However, in view of ongoing research, changes in government regulations, and the constant flow of information relating to drug therapy and drug reactions, the reader is urged to check the package inserts of all drugs for any change in indications of dosage and for added warnings and precautions. This is particularly important when the recommended agent is a new and/or infrequently employed drug.

Library of Congress Cataloging-in-Publication Data
Adams, Michael, (Date)
Pharmacology for nurses: a pathophysiologic approach / Michael Patrick Adams, Leland N. Holland, Carol Urban. — 4th ed.
p. ; cm.
Includes bibliographical references and index.
ISBN-13: 978-0-13-302618-4
ISBN-10: 0-13-302618-3
I. Holland, Leland Norman, (Date) II. Urban, Carol Q. (Carol Quam) III. Title.
[DNLM: 1. Drug Therapy—Nursing. 2. Pharmacological Phenomena—Nurses' Instruction. 3. Pharmacology—Nurses' Instruction. WB 330]
LC Classification not assigned
615'.1—dc23

2012039180

10 9 8 7 6 5 4 3 2 1

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ISBN-10: 0-13-302618-3
ISBN-13: 978-0-13-302618-4

About the Authors

Michael Patrick Adams, PhD, is an accomplished educator, author, and national speaker. The National Institute for Staff and Organizational Development in Austin, Texas, named Dr. Adams a Master Teacher. He has published two other textbooks with Pearson Publishing: *Core Concepts in Pharmacology* and *Pharmacology for Nurses: A Pathophysiologic Approach.*

Dr. Adams obtained his master's degree in pharmacology from Michigan State University and his doctorate in education from the University of South Florida. Dr. Adams was on the faculty of Lansing Community College and served as Dean of Health Professions at Pasco-Hernando Community College for 15 years. He is currently Professor of Anatomy and Physiology at St. Petersburg College.

I dedicate this book to nursing educators, who contribute every day to making the world a better and more caring place.

—MPA

Leland Norman Holland, Jr., PhD (Norm), over 20 years ago, started out like many scientists, planning for a career in basic science research. He was quickly drawn to the field of teaching in higher medical education, where he has spent most of his career since then. Among the areas where he has been particularly effective are preparatory programs in nursing, medicine, dentistry, pharmacy, and allied health. Dr. Holland is both a professor and supporter in nursing education nationwide. He brings to the profession a depth of knowledge in biology, chemistry, and medically related subjects such as microbiology, biological chemistry, and pharmacology. Dr. Holland's doctoral degree is in medical pharmacology. He is very much dedicated to the success of students and their preparation for careers in health care. He continues to motivate students in the lifelong pursuit of learning.

To the greatest family in the world, Karen, Alexandria, Caleb, and Joshua.

—LNH

Carol Quam Urban, PhD, RN, is the Assistant Dean for Undergraduate Nursing and an Assistant Professor in the School of Nursing, College of Health and Human Services, at George Mason University in Fairfax, Virginia. She has worked to develop and presents at conferences new models for RN-to-BSN education to answer the IOM's call for a seamless transition for continuing nursing education and practice. She serves on advisory boards for nurse residency programs and for community home health/hospice agencies where she also provides education on topics in pharmacology, medication reconciliation, and patient education. She has published the Pearson textbook *Pharmacology: Connections to Practice* with Dr. Adams.

To my daughter, Joy, an extraordinary and resilient young woman and future nurse. And in memory of my son, Keith, the bravest and happiest soul I know.

—CQU

Thank You

Our heartfelt thanks go out to our colleagues from schools of nursing across the country who have given their time generously to help create this exciting new medical-surgical nursing textbook. These individuals helped us plan and shape our book and resources by reviewing chapters, art, design, and more. *Pharmacology for Nurses: A Pathophysiologic Approach, Fourth Edition,* has reaped the benefit of your collective knowledge and experience as nurses and teachers, and we have improved the materials due to your efforts, suggestions, objections, endorsements, and inspiration. Among those who gave their time generously are the following:

Robin Adams-Weber, DNP, WHCNP-C, RN
Professor, Malone University
Canton, Ohio

Candyce Antley, RN, MN
Full-time Instructor, Midlands Technical College
Columbia, South Carolina

Mary Ann Balut, RN, MSN, APN
Professor, Raritan Valley Community College
Branchburg, New Jersey

Staci M. Boruff, MSN, RN
Course Coordinator, Walters State Community College
Morristown, Tennessee

Heather Campbell-Williams, MSN, RN
Professor, Oklahoma City Community College
Oklahoma City, Oklahoma

Darlene Clark, RN, MS
Course Coordinator, Penn State University
University Park, Pennsylvania

Joyce Coleman, MS, RN, WHNP-BC
Adjunct Instructor, Riverside School of Health Careers
Newport News, Virginia

Angela Collins, DSN, RN, CCNS, ACNS, BC
Professor, Capstone College of Nursing
Tuscaloosa, Alabama

Tamara Condrey, MSN, RN, ACNS-BC, CCRN
Professor, Columbus State University
Columbus, Georgia

Cynthia Cross, CCRN, APN
Professor, County College of Morris
Randolph, New Jersey

Diane Daddario, MSN, ACNS-BC, RN, BC, CMSRN
Adjunct Instructor, Pennsylvania College of Technology
Williamsport, Pennsylvania

Amanda Denno, MSN, MBA, RN
Full-time Instructor, Lakeview College of Nursing
Danville, Illinois

Sherika P. Derico, MSN, RN
Professor, Columbus State University
Columbus, Georgia

Janice Di Falco, RN, MSN, CNS, CMSRN, FAACVPR
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Pasadena, Texas

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Moberly, Missouri

Jacqueline Frock, MSN, RN
Professor, Oklahoma City Community College
Oklahoma City, Oklahoma

Yolanda Green
Professor, Chattanooga State Community College
Chattanooga, Tennessee

Sheri Gunderson, MS, RN
Full-time Instructor, Jamestown College
Jamestown, North Dakota

Carolyn E. Holl, RN, MA, CPN, CNE
Full-time Instructor, Raritan Valley Community College
Somerville, New Jersey

Monica Holland, MS, RN
Professor, Oklahoma City Community College
Oklahoma City, Oklahoma

Karen Hughes
Professor, Columbus State Community College
Columbus, Ohio

Shirley E. Keckley, RN, MSN, CNE
Professor, Columbus State Community College
Columbus, Ohio

Carol Kramme, MSN, CNE
Other, Cox College
Springfield, Missouri

Coleen Kumar, RN, MS, CNS
Professor, Kingsborough Community College
Brooklyn, New York

Cecilia Langford, EdD, MSN, ARNP, PMHNP-BC
Full-time Instructor, Florida State College
Jacksonville, Florida

Constance Lawrence, MS, FNP-BC, DNP
Adjunct Instructor, SUNY Brockport
Brockport, New York

Angela P. Lukomski, RN, DNP, CPNP
Professor, Eastern Michigan University
Ypsilanti, Missouri

Alice L. March, PhD, RN, FNP-C, CNE
Professor, The University of Alabama
Tuscaloosa, Alabama

Antoinette McCray, RNC, MSN, CNS
Full-time Instructor, Norfolk State University
Norfolk, Virginia

Susan McDonald, PhD, CPNP, CNS, RN
Full-time Instructor, Stephen F Austin State University
Nacogdoches, Texas

Bethany J. Mello, DNP, NP-c
Adjunct Instructor, Jamestown College
Jamestown, North Dakota

Mimi Merriman
Full-time Instructor, Columbus State University
Columbus, Georgia

Michelle Montpas, RN, MSN, EdD, CNE
Professor, Mott Community College
Flint, Michigan

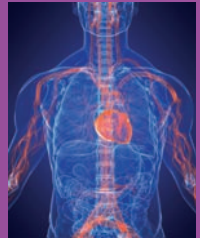
Amy Ragnone, MSN, MA, RN
Professor, College of Southern Nevada
Las Vegas, Nevada

Rose Marie Smith, RN, MS
Professor, Platt College
Oklahoma City, Oklahoma

Regina Tuma
Full-time Instructor, Cuyahoga Community College
Cleveland, Ohio

Benson Kar Leung Yeung, MSN, RN
Full-time Instructor, CSULA
Los Angeles, California

Preface



When students are asked which subject in their nursing program is the most challenging, pharmacology always appears near the top of the list. The study of pharmacology demands that students apply knowledge from a wide variety of the natural and applied sciences. Successfully predicting drug action requires a thorough knowledge of anatomy, physiology, chemistry, and pathology as well as the social sciences of psychology and sociology. Lack of adequate pharmacology knowledge can result in immediate and direct harm to the patient; thus, the stakes in learning the subject are high.

Pharmacology cannot be made easy, but it can be made understandable if the proper connections are made to knowledge learned in these other disciplines. The vast majority of drugs in clinical practice are prescribed for specific diseases, yet many pharmacology textbooks fail to recognize the complex interrelationships between pharmacology and pathophysiology. When drugs are learned in isolation from their associated diseases or conditions, students have difficulty connecting pharmacotherapy to therapeutic goals and patient wellness. The pathophysiology focus of this textbook gives the student a clearer picture of the importance of pharmacology to disease and, ultimately, to patient care. The approach and rationale of this textbook focus on a holistic perspective to patient care, which clearly shows the benefits and limitations of pharmacotherapy in curing or preventing illness. Although difficult and challenging, the study of pharmacology is truly a fascinating, lifelong journey.

NEW TO THIS EDITION

The fourth edition of *Pharmacology for Nurses: A Pathophysiologic Approach* has been thoroughly updated to reflect current pharmacologic drugs and processes.

- NEW! Evidence-Based Practice features apply medical research to pharmacology.
- NEW! Black Box Warnings issued by the FDA now appear for all appropriate drug prototypes.
- NEW! Incorporation of the QSEN competencies: The QSEN competencies related to patient-centered care, teamwork and collaboration, evidence-based practice, and patient safety are incorporated throughout the features and Nursing Process Focus charts.
- EXPANDED! Includes more than 40 new drugs, drug classes, indications, and therapies that have been approved since the last edition.
- EXPANDED! Pharmacotherapy Illustrated diagrams to help students visualize the connection between pharmacology and the patient.
- UPDATED! Nursing Process Focus charts have been revised to contain current applications to clinical practice.
- ENHANCED AND REVISED! End-of-chapter NCLEX-RN® questions now include alternative format items and complete rationales.
- REVISED! Many Mechanism in Action animations have been enhanced to identify the key drug mechanisms.

ORGANIZATION AND STRUCTURE—A BODY SYSTEM AND DISEASE APPROACH

Pharmacology for Nurses: A Pathophysiologic Approach is organized according to body systems (units) and diseases (chapters). Each chapter provides the complete information on the drug classifications used to treat the disease(s) classes. Specially designed numbered headings describe key concepts and cue students to each drug classification discussion.

The pathophysiology approach clearly places the drugs in context with how they are used therapeutically. The student is able to locate easily all relevant anatomy, physiology, pathology, and pharmacology in the same chapter in which the drugs are discussed. This approach provides the student with a clear view of the connection among pharmacology, pathophysiology, and the nursing care learned in other clinical courses.

The vast number of drugs available in clinical practice is staggering. To facilitate learning, this text uses drug prototypes in which the most representative drugs in each classification are introduced in detail. Students are less intimidated when they can focus their learning on one representative drug in each class.

Prototype Drug | Procainamide

Therapeutic Class: Class IA antidysrhythmic **Pharmacologic Class:** Sodium channel blocker

ACTIONS AND USES

Procainamide is an older drug, approved in 1950, that is chemically related to the local anesthetic procaine. Procainamide blocks sodium ion channels in myocardial cells, thus reducing automaticity and slowing conduction of the action potential across the myocardium. This slight delay in conduction velocity prolongs the refractory period and can suppress dysrhythmias. Procainamide is referred to as a broad-spectrum drug because it has the ability to correct many different types of atrial and ventricular dysrhythmias. The most common dosage form is the extended-release tablet; however, procainamide is also available in intravenous (IV) and intramuscular (IM) formulations. The therapeutic serum drug level is 4 to 8 mcg/mL. The use of procainamide has declined significantly due to the development of more specific and safer drugs.

ADMINISTRATION ALERTS

- Use the supine position during IV administration because severe hypotension may occur.
- Pregnancy category C.

PHARMACOKINETICS (PO)

Onset	Peak	Duration
immediate IV; 10–30 min IM	1–1.5 h	3–4 h

ADVERSE EFFECTS

Nausea, vomiting, abdominal pain, hypotension, and headache are common during procainamide therapy. High doses may produce CNS effects such as confusion or psychosis.

Black Box Warning: Chronic administration may result in an increased titer of antinuclear antibodies (ANAs). A lupus-like syndrome may occur in 30% to 50% of patients who are taking the drug for more than a year. Procainamide should be reserved for life-threatening dysrhythmias because it has the ability to produce new dysrhythmias or worsen existing ones. Agranulocytosis, bone marrow depression, neutropenia, hypoplastic anemia, and thrombocytopenia have been reported, usually within the first 3 months of therapy. Complete blood counts should be monitored carefully and the drug discontinued at the first sign of potential blood dyscrasia.

Contraindications: Procainamide is contraindicated in patients with complete AV block, severe HF, blood dyscrasias, and myasthenia gravis.

INTERACTIONS

Drug–Drug: Additive cardiac depressant effects may occur if procainamide is administered with other antidysrhythmics. Additive anticholinergic side effects will occur if procainamide is used concurrently with anticholinergic drugs.

Lab Tests: Procainamide may increase values for the following: AST, ALT, serum alkaline phosphatase, LDH, and serum bilirubin. False-positive Coombs test and ANA titers may occur.

Herbal/Food: Unknown.

Treatment of Overdose: Supportive treatment is targeted to reversing hypotension with vasopressors and preventing or treating procainamide-induced dysrhythmias.

This text uses several strategies to connect pharmacology to nursing practice. Throughout the text the student will find interesting features such as Complementary and Alternative Therapies, Treating the Diverse Patient, and Lifespan Considerations that clearly place the drugs in context with their clinical applications. Evidence-Based Practice features illustrate how current medical research is used to improve patient teaching.

Complementary and Alternative Therapies

Fish Oils for Inflammation

Fish oils, also known as marine oils, are lipids found primarily in coldwater fish. These oils are rich sources of long-chain polyunsaturated fatty acids of the omega-3 type. The two most studied fatty acids found in fish oils are eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). These fatty acids are known for their triglyceride-lowering activity. Several mechanisms are believed to account for the anti-inflammatory activity of EPA and DHA. The two competitively inhibit the conversion of arachidonic acid to the proinflammatory prostaglandins, thus reducing their synthesis.

Treating the Diverse Patient

Sleep Disturbance in the Patient with Alzheimer's and Parkinson's Diseases

Both Alzheimer's and Parkinson's diseases are progressive degenerative neurologic disorders and sleep disturbances are common in both conditions. Loss of sleep may increase agitation and physical symptoms and it is difficult for both the patient and the family or caregiver when the patient often awakens. Promoting good sleep hygiene is important at any age, but it is particularly important for patients where sleep disturbances are common. Strategies that may improve sleep or sleep habits include:

- Establish regular schedules of activities throughout the day for mealtimes, toileting, and short rest periods.
- When possible, provide the patient with the opportunity to see the sun or sunlight to help maintain the body's circadian rhythms.

Lifespan Considerations: Geriatric

Dental Health and Dysrhythmias in the Older Adult

Studies have begun to link poor dental health with many diseases related to inflammation. Dental caries (tooth decay) has been shown to increase inflammatory chemicals in the body and some studies link the rise of these chemical mediators to coronary heart disease. Kaneko, Yoshihara, and Miyazaki (2011) studied adults age 70 or older for a period of 4 years. For nonsmokers, an increase in the number of oral sites with periodontal disease was associated with a statistically significant elevated risk of dysrhythmias. The same increase in risk was not found among those elders who smoked, although smoking is associated with the development of periodontal disease.

While increasing age is often associated with increasing dental concerns and tooth loss, the nurse should continue to encourage the older adult to maintain adequate dental hygiene, not only as a method for preserving teeth and dental function, but as a possible preventive measure

Evidence-Based Practice

Folic Acid Supplements During Pregnancy for Mothers with Diabetes

The Question: Does the use of perinatal vitamin supplements containing folic acid reduce the incidence of birth defects in infants born to mothers with diabetes?

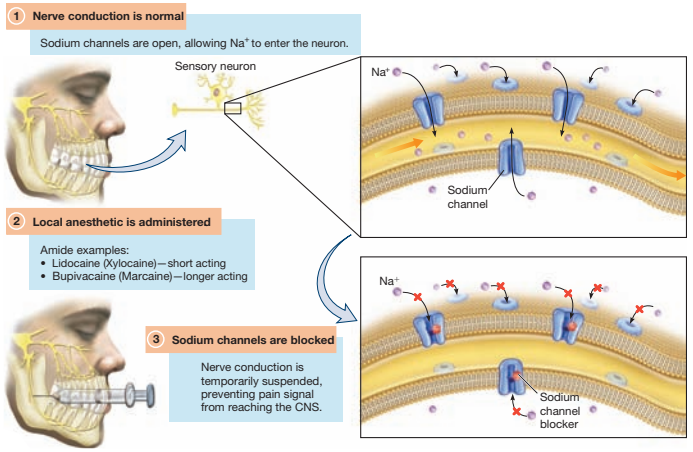
Evidence: It has been established for several decades that folic acid deficiency during pregnancy increases the risk of neural tube and other defects in the newborn, and that receiving adequate amounts of folic acid during pregnancy can reduce the risk. Women with diabetes are also at higher risk for having a child with birth defects than women without diabetes.

Correa et al. (2012) used data from the National Birth Defects Prevention Study (1997–2004) to study the pregnancy outcomes in women with diabetes (type 1 or 2) who took vitamin supplements with folic acid compared to those who took no supplements during pregnancy. Compared to women with diabetes who took such supplements, the authors estimated a twofold

Students learn better when supplied with accurate, attractive graphics and rich media resources. *Pharmacology for Nurses: A Pathophysiologic Approach* contains a generous number of figures, with an unequaled art program. Pharmacotherapy Illustrated features appear throughout the text, breaking down complex topics into easily understood formats. Animations of drug mechanisms take the student step-by-step on how drugs act.

PHARMACOTHERAPY ILLUSTRATED

19.1 Mechanism of Action of Local Anesthetics



One of the strongest components of *Pharmacology for Nurses: A Pathophysiologic Approach* is the Nursing Process Focus feature. This feature clearly and concisely relates pharmacotherapy to patient assessment, nursing diagnoses, planning patient outcomes, implementing patient-centered care, and evaluating the outcomes. Student feedback has shown that these Nursing Process Focus tables are a significant component of planning and implementing nursing care plans.

Nursing Process Focus PATIENTS RECEIVING ERYTHROPOIESIS-STIMULATING DRUGS

ASSESSMENT	POTENTIAL NURSING DIAGNOSES
Baseline assessment prior to administration: ▪ Obtain a complete health history including cardiovascular (including hypertension [HTN], MI) and peripheral vascular disease, respiratory (including previous pulmonary embolism), neurologic (including stroke), or hepatic or renal disease. Obtain a drug history including allergies, current prescription and over-the-counter (OTC) drugs, herbal preparations, and alcohol use. Be alert to possible drug interactions. ▪ Obtain baseline weight and vital signs, especially blood pressure. ▪ Evaluate appropriate laboratory findings (e.g., CBC, aPTT, INR, transferrin and serum ferritin levels, renal and liver function studies).	▪ *Ineffective Tissue Perfusion* ▪ *Activity Intolerance* ▪ *Fatigue* ▪ *Deficient Knowledge* (drug therapy) ▪ *Risk for Injury,* related to adverse drug effects
Assessment throughout administration: ▪ Continue assessment for therapeutic effects (e.g., Hct, RBC count significantly improved, patient's activity level and general sense of well-being have improved). ▪ Continue frequent monitoring of appropriate laboratory values (e.g., CBC, aPTT, INR). ▪ Monitor vital signs frequently, especially blood pressure, during the first 2 weeks of therapy. ▪ Assess for adverse effects: HTN, headache, neurologic changes in level of consciousness or premonitory signs and symptoms of seizure activity, angina, and signs of thrombosis development in peripheral extremities.	
PLANNING: PATIENT GOALS AND EXPECTED OUTCOMES	

No pharmacology text is complete unless it contains a method of self-assessment by which students may gauge their progress. *Pharmacology for Nurses: A Pathophysiologic Approach* contains an end-of-chapter review of the major concepts. NCLEX-RN® and case study questions, with the answers provided, allow students to check their retention of chapter material.

Chapter Review

KEY CONCEPTS

The numbered key concepts provide a succinct summary of the important points from the corresponding numbered section within the chapter. If any of these points are not clear, refer to the numbered section within the chapter for review.

29.1 The frequency of dysrhythmias in the population is difficult to predict because many patients experience no symptoms. Persistent or severe dysrhythmias may be lethal. Dysrhythmias are classified by the location (atrial or ventricular) or type (flutter, fibrillation, or block) of rhythm abnormality produced.

29.6 Antidysrhythmic drugs are classified by their mechanism of action, namely, classes I through IV. The use of antidysrhythmic drugs has been declining.

29.7 Sodium channel blockers, the largest group of antidysrhythmics, act by slowing the rate of impulse conduction across the heart.

ACKNOWLEDGMENTS

When authoring a textbook like this, many dedicated and talented professionals are needed to bring the vision to reality. Pamela Fuller, Executive Acquisitions Editor, is responsible for guiding the many details in the production of the fourth edition. Our Development Editors, Laura Horowitz and Anne Seitz, supplied the expert guidance and leadership to keep everyone on track and be certain our project would be created on time. Providing the expertise for our comprehensive supplement package was Nicole Coady.

The superb design staff at Pearson, especially Chris Weigand, created wonderful text and cover designs. The production process was guided by Production Editor Cathy O'Connell. Mary Tindle and her colleagues at S4Carlisle provided expert, professional guidance in all aspects of the art and production process.

Although difficult and challenging, the study of pharmacology is truly a fascinating lifelong journey. We hope we have succeeded in writing a textbook that makes that study easier and more understandable so that nursing students will be able to provide safe, effective nursing care to patients who are undergoing drug therapy. We hope students and faculty will share with us their experiences using this textbook and all its resources.

Contents

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Unit 1

Core Concepts

Chapter 1

Introduction to Pharmacology

Learning Outcomes

After reading this chapter, the student should be able to:

1. Identify key events in the history of pharmacology.
2. Explain the interdisciplinary nature of pharmacology, giving an example of how knowledge from different sciences impacts the nurse's role in drug administration.
3. Compare and contrast therapeutics and pharmacology.
4. Compare and contrast traditional drugs, biologics, and complementary and alternative medicine (CAM) therapies.
5. Outline the major differences between prescription and over-the-counter (OTC) drugs.
6. Identify key U.S. drug regulations that have ensured the safety and efficacy of medications.
7. Discuss the role of the U.S. Food and Drug Administration (FDA) in the drug approval process.
8. Explain the four phases of approval for therapeutic and biologic drugs.
9. Discuss how the FDA has increased the speed with which new drugs reach consumers.
10. Identify the nurse's role in the drug approval process and in maintaining safety practices.

Key Terms

biologics *page 4*
black box warnings *page 6*
boxed warnings *page 6*
clinical investigation *page 8*
clinical phase trials *page 8*
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More drugs are being administered to patients than ever before. More than 3 billion prescriptions are dispensed each year in the United States. About one half of all Americans take one prescription drug regularly and one out of six persons takes at least three prescription drugs. The purpose of this chapter is to introduce the subject of pharmacology and to emphasize the role of government in ensuring that drugs, herbals, and other natural alternatives are safe and effective for public use. The chapter also serves as a starting point for connections between important introductory pharmacologic concepts and nursing practice.

1.1 History of Pharmacology

The story of pharmacology is rich and exciting, filled with accidental discoveries and landmark events. Its history likely began when humans first used plants to relieve symptoms of disease. One of the oldest forms of health care, herbal medicine has been practiced in virtually every culture dating to antiquity. The Babylonians recorded the earliest surviving "prescriptions" on clay tablets in 3000 B.C. At about the same time, the Chinese recorded the *Pen Tsao* (Great Herbal), a 40-volume compendium of plant remedies dating to 2700 B.C. The Egyptians followed in 1500 B.C. by archiving their remedies on a document known as the *Eber's Papyrus*.

Little is known about pharmacology during the Dark Ages. Although it is likely that herbal medicine continued to be practiced, few historical events related to this topic were recorded. Pharmacology, and indeed medicine, could not advance until the discipline of science was eventually viewed as legitimate by the religious doctrines of the era.

The first recorded reference to the word *pharmacology* was found in a text entitled "Pharmacologia sen Manuductio and Materiam Medicum," by Samuel Dale, in 1693. Before this date, the study of herbal remedies was called "Materia Medica," a term that persisted into the early 20th century.

Although the exact starting date is obscure, modern pharmacology is thought to have begun in the early 1800s. At that time, chemists were making remarkable progress in isolating specific substances from complex mixtures. This enabled scientists to isolate the active agents morphine, colchicine, curare, cocaine, and other early pharmacologic agents from their natural sources. Using standardized amounts, pharmacologists could then study their effects in animals more precisely. Indeed, some of the early researchers used themselves as test subjects. Friedrich Serturner, who first isolated morphine from opium in 1805, injected himself and three friends with a huge dose (100 mg) of his new product. He and his colleagues suffered acute morphine intoxication for several days afterward.

Pharmacology as a distinct discipline was officially recognized when the first department of pharmacology was established in Estonia in 1847. John Jacob Abel, who is considered the father of American pharmacology owing to his many contributions to the field, founded the first pharmacology department in the United States at the University of Michigan in 1890.

In the 20th century, the pace of change in all areas of medicine continued exponentially. Pharmacologists no longer needed to rely on the slow, laborious process of isolating active agents from scarce natural sources; they could synthesize drugs in the laboratory. Hundreds of new drugs could be synthesized and tested in a relatively short time. More importantly, it became possible to understand how drugs produced their effects, down to their molecular mechanism of action.

The current practice of pharmacology is extremely complex and far advanced compared with its early, primitive history. The nurse who consults with a pharmacist in the use of pharmacologic substances and other health professionals who practice it must never forget its early roots: the application of products to relieve human suffering. Whether a substance is extracted from the Pacific yew tree, isolated from a fungus, or created totally in a laboratory, the central purpose of pharmacology is to focus on the patient and to improve the quality of life.

1.2 Pharmacology: The Study of Medicines

The word **pharmacology** is derived from two Greek words: *pharmakon,* which means "medicine," and *logos,* which means "study." Thus, pharmacology is most simply defined as the study of medicine. Pharmacology is an expansive subject ranging from understanding how drugs are administered, to where they travel in the body, to the actual responses produced. To learn the discipline well, nursing students must acquire a broad knowledge base from various foundation areas such as anatomy and physiology, chemistry, microbiology, and pathophysiology.

As an example, aminoglycosides are a class of antibiotics that are useful in the treatment of many infectious diseases. The mainstay of treatment for infective endocarditis is antibiotic therapy, and this is instituted as soon as possible to minimize valvular damage. Caution must be used, however, because some aminoglycosides can cause inner ear toxicity and neuromuscular impairment, especially if furosemide (a loop diuretic) is administered at the same time. You can see how, in this case, concepts from multiple science disciplines are integrated. A knowledge of chemistry would be implied by the terms *amino* and *glyco*. Further study about "infectives" would draw much information from the subject of microbiology including antibiotics and sensitivities to gram-positive and gram-negative bacteria. The fields of anatomy and physiology would correlate much information with emphasis on ear anatomy and organs of the muscular, nervous, renal, and cardiovascular systems. "Endocarditis" would be the central pathophysiological focus of treatment. Most of the time pharmacology incorporates knowledge from multiple areas, which health care providers use in making decisions about drug administration.

More than 10,000 brand-name drugs, generic drugs, and combination drugs are currently available. Each has its own characteristic set of therapeutic applications, interactions, side effects, and mechanisms of action. Many drugs are prescribed for more than one disease, and most produce multiple effects within the body. Drugs may elicit different responses depending on individual patient factors such as age, sex, body mass, health status, and genetics. Indeed, learning the applications of existing medications and staying current with new drugs introduced every year are among the formidable but necessary tasks for the nurse. These challenges, however, are critical for both the patient and the health care practitioner. If applied properly, drugs can dramatically improve the quality of life. If applied improperly, drugs can produce devastating consequences.

1.3 Pharmacology and Therapeutics

It is obvious that a thorough study of pharmacology is important to health care providers who prescribe drugs on a daily basis. The nurse is often the health care provider most directly involved with patient care and is active in educating, managing, and monitoring the proper use of drugs. This applies not only to nurses in clinics, hospitals, and home health care settings but also to nurses who teach and to students entering the nursing profession. In all these cases, it is necessary that individuals have a thorough knowledge of pharmacology to perform their duties. As nursing students progress toward their chosen specialty, pharmacology is at the core of patient care and is integrated into every step of the nursing process. Learning pharmacology is a gradual, continuous process that does not end with graduation. One never completely masters every facet of drug action and application. That is one of the motivating challenges of the nursing profession.

Another important area of study for the nurse, sometimes challenging to distinguish from pharmacology, is the study of therapeutics. Therapeutics is slightly different from the field of pharmacology, although the disciplines are closely connected. **Therapeutics** is the branch of medicine concerned with the prevention of disease and treatment of suffering. **Pharmacotherapy,** or *pharmacotherapeutics,* is the application of drugs for the purpose of disease prevention and the treatment of suffering. Drugs are just one of many tools available to the nurse for these purposes.

1.4 Classification of Therapeutic Agents as Drugs, Biologics, and Complementary and Alternative Medicine Therapies

Substances applied for therapeutic purposes fall into one of the following three general categories:

- Drugs or medications.
- Biologics.
- Complementary and alternative medicine (CAM) therapies.

A **drug** is a chemical agent capable of producing biologic responses within the body. These responses may be desirable (therapeutic) or undesirable (adverse). After a drug is administered, it is called a **medication.** From a larger perspective, drugs and medications may be considered a part of the body's normal activities, from the essential gases that we breathe to the foods that we eat. Because drugs are defined so broadly, it is necessary to clearly distinguish them from other substances such as foods, household products, and cosmetics. Many agents such as antiperspirants, sunscreens, toothpaste, and shampoos might alter the body's normal activities, but they are not necessarily considered medically therapeutic, as are drugs.

Although most modern drugs are synthesized in a laboratory, **biologics** are agents naturally produced in animal cells, by microorganisms, or by the body itself. Examples of biologics include hormones, monoclonal antibodies, natural blood products and components, interferons, and vaccines. Biologics are used to treat a wide variety of illnesses and conditions.

Other therapeutic approaches include **complementary and alternative medicine (CAM) therapies.** These involve natural plant extracts, herbs, vitamins, minerals, dietary supplements, and many techniques considered by some to be unconventional. Such therapies include manipulative and body-based practices such as acupuncture, hypnosis, biofeedback, and massage. Because of their great popularity, herbal and alternative therapies are featured throughout this text wherever they show promise in treating a disease or condition. Herbal therapies are presented in chapter 10 ⇨.

1.5 Prescription and Over-the-Counter Drugs

Legal drugs are obtained either by a prescription or over the counter (OTC). There are major differences between the two methods of dispensing drugs. To obtain prescription drugs, the person must receive a written order from a person with the legal authority to write such a prescription. The advantages to requiring an authorization are numerous. The health care provider or nurse practitioner has an opportunity to examine the patient and determine a specific diagnosis. The practitioner can maximize therapy by ordering the proper drug for the patient's condition and by conveying the amount and frequency of drug to be dispensed. In addition, the health care provider has an opportunity to teach the patient the proper use of the drug and what side effects to expect. In a few instances, a high margin of safety observed over many years can prompt a change in the status of a drug from prescription to OTC.

In contrast to prescription drugs, OTC drugs do not require a health care provider's order. In most cases, patients may treat themselves safely if they carefully follow instructions included with the medication. If patients do not follow these guidelines, OTC drugs can have serious adverse effects.

Patients prefer to take OTC drugs for many reasons. They are obtained more easily than prescription drugs. No

appointment with a health care provider is required, thus saving time and money. Without the assistance of a health care provider, however, choosing the proper drug for a specific problem can be challenging for a patient. OTC drugs may react with foods, herbal products, prescription medications, or other OTC drugs. Patients may not be aware that some OTC drugs can impair their ability to function safely. Self-treatment is sometimes ineffectual, and the potential for harm may increase if the disease is allowed to progress.

1.6 Drug Regulations and Standards

Until the 19th century, there were few standards or guidelines in place to protect the public from drug misuse. The archives of drug regulatory agencies are filled with examples of early medicines, including rattlesnake oil for rheumatism; epilepsy treatment for spasms, hysteria, and alcoholism; and fat reducers for a slender, healthy figure. Many of these early concoctions proved ineffective, though harmless. At their worst, some contained hazardous levels of dangerous or addictive substances. It became quite clear that drug regulations were needed to protect the public.

The first standard commonly used by pharmacists was the **formulary,** or list of drugs and drug recipes. In the United States, the first comprehensive publication of drug standards, called the *U.S. Pharmacopoeia* (*USP*), was established in 1820. A **pharmacopoeia** is a medical reference summarizing standards of drug purity, strength, and directions for synthesis. In 1852, a national professional society of pharmacists called the American Pharmaceutical Association (APhA) was founded. From 1852 to 1975, two major compendia maintained drug standards in the United States: the *U.S. Pharmacopoeia,* and the *National Formulary* (*NF*) established by the APhA. All drug products were covered in the *USP;* pharmaceutical ingredients were covered in the *NF.* In 1975, the two entities merged into a single publication, the *U.S. Pharmacopoeia–National Formulary* (*USP-NF*). USP-NF is an annual publication, comprising one main publication and two supplements each year. Today, the USP label can be found on many medications verifying the purity and exact amounts of ingredients found within the container. Sample labels are illustrated in ▲ Figure 1.1.

In the early 1900s, the United States began to develop and enforce tougher drug legislation to protect the public. In 1902, the Biologics Control Act helped to standardize the quality of serums and other blood-related products. The Pure Food and Drug Act of 1906 gave the government power to control the labeling of medicines. In 1912, the Sherley Amendment prohibited the sale of drugs labeled with false therapeutic claims that were intended to defraud the consumer. In 1938, Congress passed the Food, Drug, and Cosmetic Act. This was the first law preventing the sale of drugs that had not been thoroughly tested before marketing. Later amendments to this law required drug companies to prove the safety and efficacy of any drug before it could be sold within the United States. In reaction to the rising popularity of dietary supplements, Congress passed the Dietary Supplement Health and Education Act of 1994 in an attempt to control misleading industry claims. A brief time line of major events in U.S. drug regulation is shown in ▲ Figure 1.2.

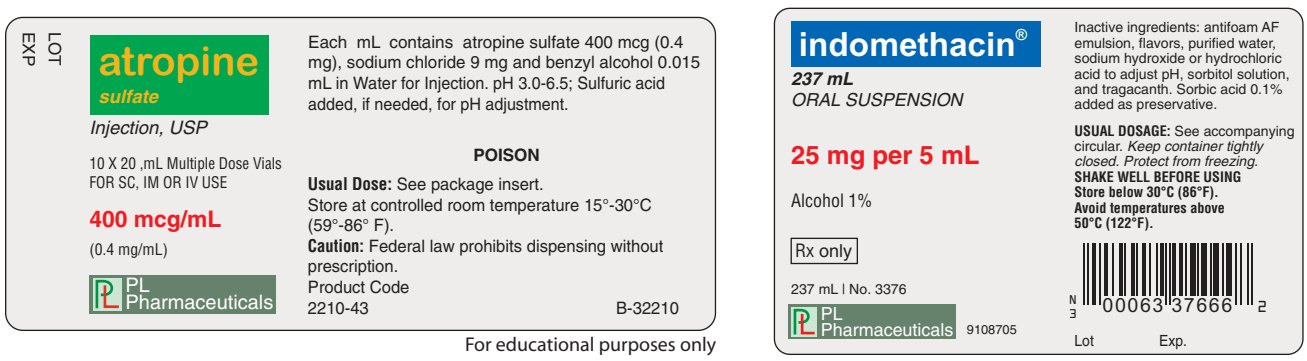
Weblink: US Pharmacopeia

Weblink: The American Pharmaceutical Association

PharmFacts

Consumer Spending on Prescription Drugs

- Spending on prescription drugs accounts for over 10% of national health spending.
- At the turn of the 21st century (1999–2009), prescription drug expenditures increased by more than 39% while the population only grew 9%.
- The average number of prescription drugs taken per patient over the course of a year is about 13 compared to 8 prescriptions per person in the mid-1990s.
- In 2010, consumers in the United States spent nearly 1.8% of their per capita gross domestic product on prescription drugs and 2.3% of their per capita personal income after taxes.
- Total pharmaceutical expenditures in the United States increased from $284 billion in 2008 to over $307 billion in 2010.



For educational purposes only

▲ ***Figure 1.1*** Medication with the USP label (left) and without USP label (right)
Practice Label "for educational purposes only."

Weblink: Agency for Healthcare Research and Quality

Weblink: FDA, Department of Health and Human Services

TIME LINE	REGULATORY ACTS, STANDARDS, AND ORGANIZATIONS
1820	A group of health care providers established the first comprehensive publication of drug standards called the **U.S. Pharmacopoeia (USP)**.
1852	A group of pharmacists founded a national professional society called the **American Pharmaceutical Association (APhA)**. The APhA then established the **National Formulary (NF)**, a standardized publication focusing on pharmaceutical ingredients. The *USP* continued to catalogue all drug-related substances and products.
1862	This was the beginning of the **Federal Bureau of Chemistry**, established under the administration of President Lincoln. Over the years and with added duties, it gradually became the Food and Drug Administration (FDA).
1902	Congress passed the **Biologics Control Act** to control the quality of serums and other blood-related products.
1906	**The Pure Food and Drug Act** gave the government power to control the labeling of medicines.
1912	**The Sherley Amendment** made medicines safer by prohibiting the sale of drugs labeled with false therapeutic claims.
1938	Congress passed the **Food, Drug, and Cosmetic Act**. It was the first law preventing the marketing of drugs not thoroughly tested. This law now provides for the requirement that drug companies must submit a New Drug Application (NDA) to the FDA prior to marketing a new drug.
1944	Congress passed the **Public Health Service Act**, covering many health issues including biologic products and the control of communicable diseases.
1975	The *U.S. Pharmacopoeia* and *National Formulary* announced their union. The **USP-NF** became a single standardized publication.
1986	Congress passed the **Childhood Vaccine Act.** It authorized the FDA to acquire information about patients taking vaccines, to recall biologics, and to recommend civil penalties if guidelines regarding biologic use were not followed.
1988	The **FDA** was officially established as an agency of the **U.S. Department of Health and Human Services**.
1992	Congress passed the **Prescription Drug User Fee Act.** It required that nongeneric drug and biologic manufacturers pay fees to be used for improvements in the drug review process.
1994	Congress passed the **Dietary Supplement Health and Education Act** that requires clear labeling of dietary supplements. This act gives the FDA the power to remove supplements that cause a significant risk to the public.
1997	The **FDA Drug Modernization Act** reauthorized the Prescription Drug User Fee Act. This act represented the largest reform effort of the drug review process since 1938.
2002	The **Bioterrorism Act** implemented guidelines for registration of selected toxins that could pose a threat to human, animal, or plant safety and health.
2007	The **FDA Amendments Act** reviewed, expanded, and reaffirmed legislation to allow for additional comprehensive reviews of new drugs and medical products. This extended the reforms imposed from 1997. The **FDA's Critical Path Initiative** was a part of this reform.
2011	Provisions of the **Health Care Reform** law allowed the FDA to approve generic versions of biologic drugs. Additional drug rebates and benefits were provided to the American public. The **FDA Food Safety Modernization Act** represents the largest reform effort of food safety review since 1938.

▲ ***Figure 1.2*** A historical time line of regulatory acts, standards, and organizations

1.7 The Role of the Food and Drug Administration

Much has changed in the regulation of drugs in the past 100 years. In 1988, the **Food and Drug Administration (FDA)** was officially established as an agency of the U.S. Department of Health and Human Services. The Center for Drug Evaluation and Research (CDER), a branch of the FDA, exercises control over whether prescription drugs and OTC drugs may be used for therapy. The CDER states its mission as facilitating the availability of safe, effective drugs; keeping unsafe or ineffective drugs off the market; improving the health of Americans; and providing clear, easily understandable drug information for safe and effective use. Any pharmaceutical laboratory, whether private, public, or academic, must solicit FDA approval before marketing a drug.

In 1997, the FDA created **boxed warnings** in order to regulate drugs with "special problems." At the time no precedent had been established to monitor drugs with a potential for causing death or serious injury. **Black box warnings,** named after the black box appearing around drug safety information located within package inserts,

eventually became one of the primary alerts for identifying extreme adverse drug reactions discovered during and after the review process. It would be ideal if all of the potential adverse effects were identified before a drug goes to the market. Because this is not realistic, nurses must be increasingly mindful about the standards of care necessary to promote safety, including scanning of medications, medication reconciliation, and special alerts. Black box warnings are included throughout this text, for all prototype drugs.

Another branch of the FDA, the Center for Biologics Evaluation and Research (CBER), regulates the use of biologics including serums, vaccines, and blood products. One historical achievement involving biologics was the 1986 Childhood Vaccine Act. This act authorized the FDA to acquire information about patients taking vaccines, to recall biologics, and to recommend civil penalties if guidelines regarding biologics were not followed.

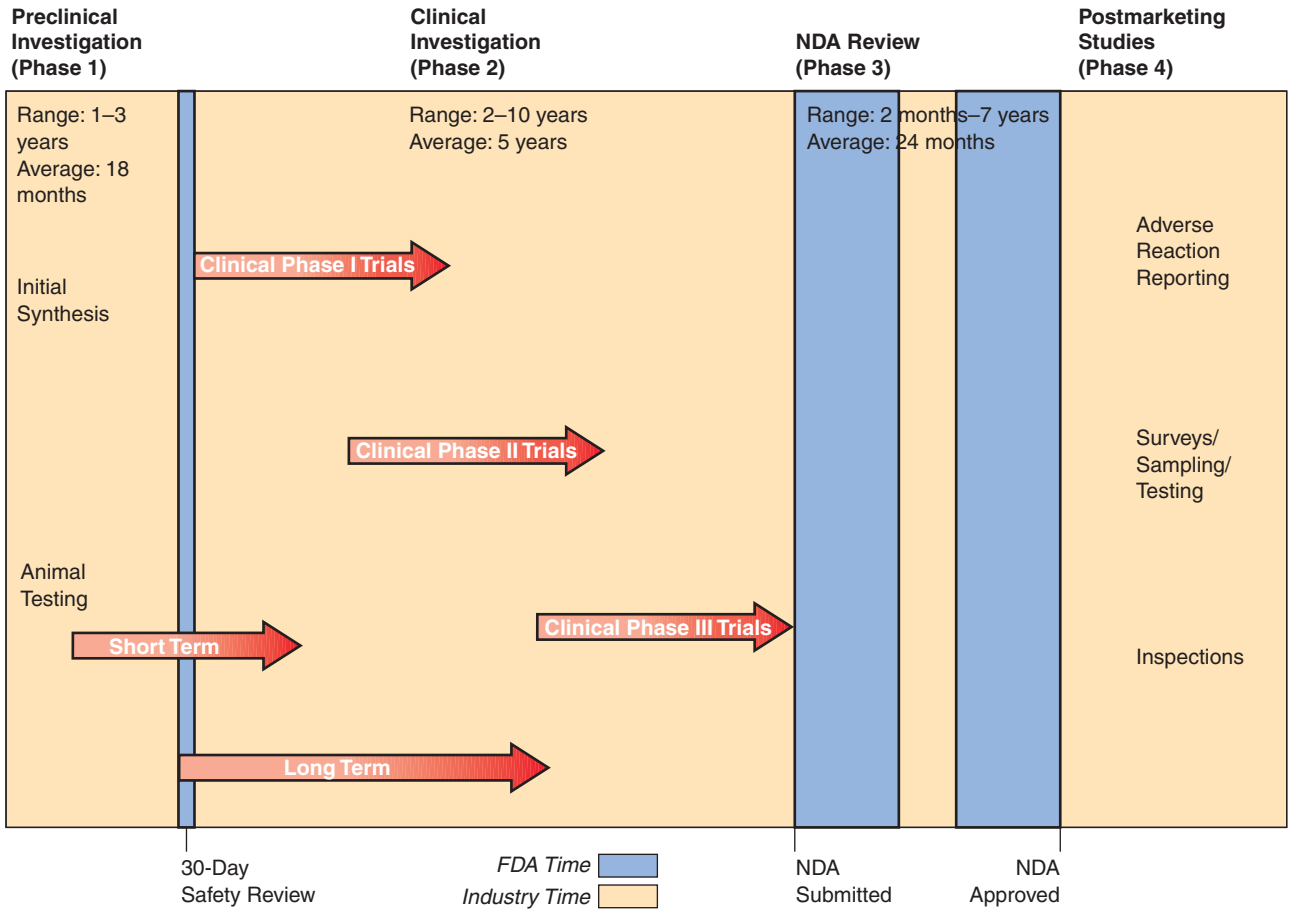
The FDA oversees administration of herbal products and dietary supplements through the Center for Food Safety and Applied Nutrition (CFSAN). Herbal products and dietary supplements are regulated by the Dietary Supplement Health and Education Act of 1994. This act does not provide the same degree of protection for consumers as the Food, Drug, and Cosmetic Act of 1938. For example, herbal and dietary supplements can be marketed without prior approval from the FDA; however, all package inserts and information are monitored once products have gone to market. The Dietary Supplement Health and Education Act is discussed in more detail in chapter 10 ⛓.

In 1998, the National Center for Complementary and Alternative Medicine (NCCAM) was established as the federal government's lead agency for scientific research and information about CAM therapies. Its mission is "to define, through rigorous scientific investigation, the usefulness and safety of complementary and alternative medicine interventions and their roles in improving health and health care." Among several areas of focus, this agency supports research and serves as a resource for nurses in establishing which CAM therapies are safe and effective.

1.8 Phases of Approval for Therapeutic and Biologic Drugs

The amount of time spent by the FDA in the review and approval process for a particular drug depends on several checkpoints along with a well-developed and organized plan. Therapeutic drugs and biologics are reviewed in four phases. These phases, summarized in ▲ Figure 1.3, are as follows:

1. Preclinical investigation.
2. Clinical investigation.
3. Review of the New Drug Application (NDA).
4. Postmarketing surveillance.



▲ *Figure 1.3* A new drug development time line with the four phases of drug approval

Preclinical investigation involves extensive laboratory research. Scientists perform many tests on human and microbial cells cultured in the laboratory. Studies are performed in several species of animals to examine the drug's effectiveness at different doses and to look for adverse effects. Extensive testing on cultured cells and in animals is essential because it allows the pharmacologist to predict whether the drug will cause harm to humans. Because laboratory tests do not always reflect the way a human responds, preclinical investigation results are always inconclusive. Animal testing may overestimate or underestimate the actual risk to humans.

In January 2007, the FDA restated its concern that a number of innovative and critical medical products had decreased since the 1990s. The **FDA's Critical Path Initiative** was an effort to modernize the sciences to enhance the use of bioinformation to improve the "safety, effectiveness, and manufacturability of candidate medical products." Listed areas of improvement were the fields of genomics and proteonomics, imaging, and bioinformatics.

Clinical investigation, the second phase of drug testing, takes place in three different stages termed **clinical phase trials.** Clinical phase trials are the longest part of the drug approval process. Clinical pharmacologists first perform tests on volunteers to determine proper dosage and to assess for adverse effects. Large groups of selected patients with the particular disease are then given the medication. Clinical investigators from different medical specialties address concerns such as whether the drug is effective, worsens other medical conditions, interacts unsafely with existing medications, or affects one type of patient more than others.

Clinical phase trials are an essential component of drug evaluations due to the variability of responses among patients. If a drug appears to be effective and without causing serious side effects, approval for marketing may be accelerated, or the drug may be used immediately in special cases with careful monitoring. If the drug shows promise but precautions are noted, the process is delayed until the pharmaceutical company remedies the concerns. In any case, a New Drug Application (NDA) must be submitted before a drug is allowed to proceed to the next phase of the approval process. An **Investigational New Drug Application (IND)** may be submitted for Phase I clinical trials when it is determined that there are significant therapeutic benefits, and that the product is reasonably safe for initial use in humans (e.g., patients who are HIV positive). Companies usually begin developing a brand name for drugs during Phase I of the IND process.

The **NDA review** is the third phase of the drug approval process. During this phase, the drug's brand name is finalized. Clinical Phase III trials and animal testing may continue depending on the results obtained from preclinical testing. By law, the FDA is permitted 6 months to initially review an NDA. If the NDA is approved, the process continues to the final phase. If the NDA is rejected, the process is suspended until noted concerns are addressed by the pharmaceutical company. The average NDA review time for new drugs is approximately 17 to 24 months.

Postmarketing surveillance, the final phase of the drug approval process, begins after clinical trials and the NDA review have been completed. The purpose of this phase is to survey for harmful drug effects in a larger population. Some adverse effects take longer to appear and are not identified until a drug is circulated to large numbers of people. Examples of this process have been approval of the COX-2 selective nonsteroidal anti-inflammatory drugs (NSAIDs), which were evaluated by the FDA during 2004 and 2005. Manufacturers of valdecoxib (Bextra), celecoxib (Celebrex), and rofecoxib (Vioxx) were originally asked to revise their labeling owing to emerging concerns that some NSAIDs exhibited extreme cardiovascular and gastrointestinal risks. In September 2004, manufacturers of rofecoxib voluntarily withdrew their product from the market due to safety concerns of heart attack and stroke. In April 2005, the FDA asked the manufacturers of valdecoxib to remove their product from the market due to similar concerns. Although celecoxib remained on the market, the FDA announced that it would continue to analyze reports to determine whether additional regulatory action would be needed. The black box warning continues to warn patients that fatal cardiovascular disease, bleeding ulceration, and serious gastrointestinal reactions may result if certain precautions are not taken.

The FDA holds public meetings annually to receive feedback from patients and professional and pharmaceutical organizations regarding the effectiveness and safety of new drug therapies. If the FDA discovers a serious problem, it will mandate that the drug be withdrawn from the market. The FDA has a free e-mail subscription service to alert the consumer regarding drugs and products withdrawn from the market. MedWatch (www.fda.gov/Safety/MedWatch) and Drug Safety Communications, Podcasts, and Newsletters sponsored by the FDA (http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/default.htm) continue to alert patients, consumers, and health care providers of drug risks. They also provide safety sheets, press announcements, and other pertinent drug fact information.

1.9 Changes to the Drug Approval Process

The process of isolating or synthesizing a new drug and testing it in cells, experimental animals, and humans can take many years. The NDA can include dozens of volumes of experimental and clinical data that must be examined in the drug review process. Some NDAs contain more than 100,000 pages. Even after all experiments have been concluded and clinical data have been gathered, the FDA review process can take several years.

Expenses associated with development of a new drug can cost pharmaceutical manufacturers millions of dollars. A recent study estimated the cost to bring a new drug to market at $802 million. These companies are often critical of the

Evidence-Based Practice

Informed Consent Procedures

Clinical Question: How can nurses assist in the informed consent procedures for patients considering participation in a clinical drug research trial?

Evidence: At some point in a nurse's career, he or she may care for a patient who is enrolled in, or considering participation in, a clinical drug research trial. The publication of the Belmont Report by the National Institutes of Health (Office of Human Subjects Research, 1979) provided guidance and principles for obtaining informed consent from patients enrolled in clinical trials. The FDA recently updated current regulations for obtaining informed consent to ensure greater transparency by making all participants aware that information about the trial would be submitted to a searchable, national databank (FDA Informed Consent Elements, 2011). Although providing the information about the research trial is beyond the scope of nursing practice and the responsibility of the researcher and health care provider, nurses can participate by helping to ensure that the patient has had any questions or concerns regarding participation addressed before signing the informed consent document. Special populations require careful assessment of the patient's ability to understand or make informed decisions about research participation. These populations may include children, patients with cognitive or mental impairments, and patients with sensory or language barriers. Cook, Moore-Cox, Xavier, Lauzier, and Roberts (2008) describe other circumstances in which obtaining informed consent for research participation is made more difficult. Situations in which the patient may be critically ill or suffering from a traumatic injury may delay obtaining consent directly from the patient and result in the patient's exclusion from the clinical trial. And differences in cultural background and beliefs about what is appropriate for a patient to know may run counter to the established guidelines that informed consent includes providing the patient with the information necessary to make an informed decision to participate.

Nursing Implications: Ensuring that a patient, family, or legal guardians have the information necessary to make informed decisions is a potential role for the nurse when caring for patients considering or participating in a clinical research trial. Whereas providing the information is beyond the scope of most nursing practice, the patient will often ask questions of the nurse and the nurse can relay these questions to the health care provider. This is especially important when working with patients or families who may have special needs, such as language or cultural differences, or in emergency situations, in which the patient is not able to receive the information and a family member or legal guardian must make the decision.

Lifespan Considerations: Geriatric

Prescription Drug Costs and the "Doughnut Hole" for Senior Citizens

In January 2006, prescription drug coverage through Medicare Part D went into effect, in part to help protect senior citizens (those over age 65) from catastrophic drug expenditures. Americans older than age 65 constitute only 13% of the population but account for about 34% of all prescriptions dispensed and 40% of all OTC medications. More than 80% of all seniors take at least one prescribed medication each day. The average older adult takes more than four prescription medications, plus two OTC medications. Many of these medicines—such as those for diabetes, hypertension, and heart disease—are taken on a permanent basis.

While Medicare Part D did make some substantial differences in helping seniors pay for their medications, a coverage gap has occurred when drug spending totals are between approximately $2,800 and $6,400. This gap has been termed the "doughnut hole" and studies have suggested that seniors reaching that doughnut hole reduce spending on their medications by 14% to 40%, depending on whether they have additional insurance coverage. With most seniors taking daily medications for chronic conditions, this decrease in spending may cause seniors to forego needed medications. The U.S. Affordable Care Act of 2010 included benefits to reduce this gap in coverage for seniors with the goal of closing it completely. Nurses should include questions about the ability to afford medications as part of taking an adequate drug history, especially when working with older adult patients.

regulatory process and are anxious to get the drug marketed to recoup their research and development expenses. The public is also anxious to receive new drugs, particularly for diseases that have a high mortality rate. Although the criticisms of manufacturers and the public are certainly understandable—and sometimes justified—the fundamental priority of the FDA is to ensure that drugs are safe. Without an exhaustive review of scientific data, the public could be exposed to dangerous medications or those that are ineffective in treating disease.

In the early 1990s, owing to pressures from organized consumer groups and various drug manufacturers, governmental officials began to plan how to speed up the drug review process. Reasons identified for the delay in the FDA drug approval process included outdated guidelines, poor communication, and insufficient staff to handle the workload.

In 1992, FDA officials, members of Congress, and representatives from pharmaceutical companies negotiated the Prescription Drug User Fee Act on a 5-year trial basis. This act required drug and biologic manufacturers to provide yearly product user fees. This added income allowed the FDA to hire more employees and to restructure its organization to more efficiently handle the processing of a greater number of drug applications. The result of restructuring was a resounding success. From 1992 to 1996, the FDA approved double the number of drugs while cutting some review times by as much as half. In 1997, the FDA Modernization Act reauthorized the Prescription Drug User Fee Act. Nearly 700 employees were added to the FDA's drug and biologics program, and more than $300 million was collected in user fees. The FDA Amendments Act expanded the reform effort in 2007 by allowing more U.S. resources to be used for comprehensive reviews of new drugs. In 2008, the target base revenue for new drugs was over $392 million. In 2011, the FDA expanded its reviews of drugs and legislation. Congress passed into law the FDA Food Safety Modernization Act to give the Department of Health and Human Services greater authority to recall certain potentially tainted products and to detect food-related illnesses and outbreaks.

1.10 Nurses, the Drug Approval Process, and the Need for Effective Safety Practices

In nursing, it is during the postmarketing surveillance period (Phase 4) that the nurse has the most frequent opportunities to participate in the drug approval process. While