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EDITION
11

PHARMACOLOGY

A PATIENT-CENTERED NURSING PROCESS APPROACH

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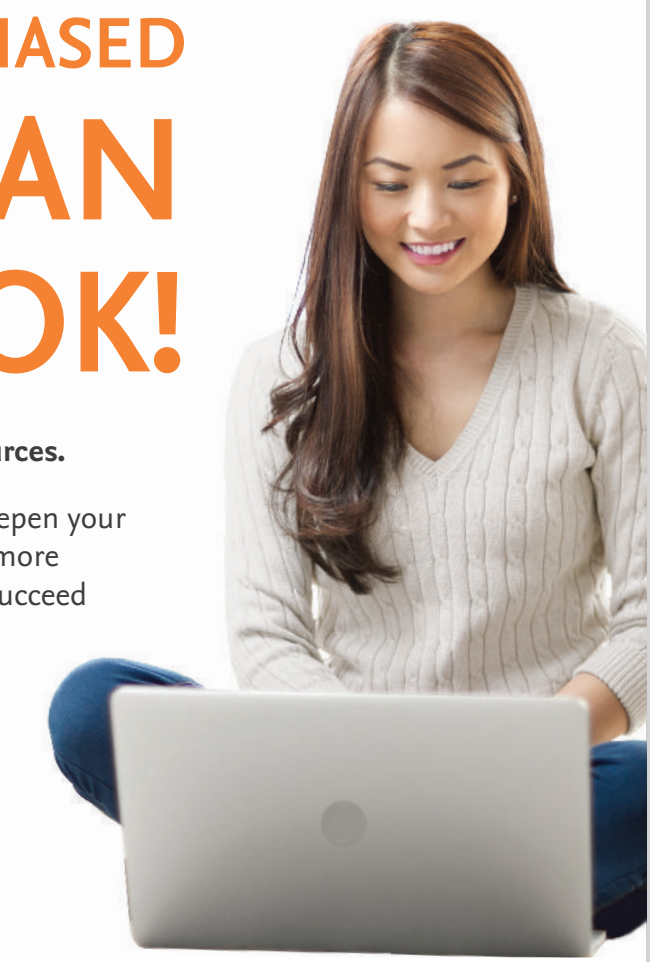

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BRIEF CONTENTS

PHARMACOLOGY

EDITION 11

A PATIENT-CENTERED NURSING PROCESS APPROACH

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St. Louis, Missouri 63043

PHARMACOLOGY: A PATIENT-CENTERED NURSING PROCESS APPROACH,
ELEVENTH EDITION ISBN: 978-0-323-79315-5

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Director, Content Development: Laurie Gower
Senior Content Strategist: Yvonne Alexopoulos
Senior Content Development Manager: Luke Held
Publishing Services Manager: Catherine Jackson
Senior Project Manager: Kate Mannix
Design Direction: Brian Salisbury

Printed in the United States

Last digit is the print number: 9 8 7 6 5 4 3 2 1

To Joyce LeFever Kee, who originated this book;
to Evelyn R. Hayes for her previous contributions to the book;
to Dr. Gerald DeLuca and Sister Bernardino Hill for their expert guidance;
and in loving memory of my parents, Otto and Pauline Schmidt, my sisters,
Katrina Sue Benge, Christina Ann Milner, and my brother, Enno Schmidt.

Linda E. McCuistion

To my daughters, Christy, Maria, and Katie; my grandchildren,
Chloe, Sofia, Catherine, Mia, Jack, and Elaine; my great-grandaughter,
Gralynn; my dear friend, Linda; and the Department of Nursing at the University
of Holy Cross, New Orleans.

Kathleen Vuljoin DiMaggio

To my Lord and Savior for His gift of nursing and teaching;
to my husband, Dr. Richard A. Winton for his continual
love and support; to my daughters, Lin and Kristin; and in
loving memory of my parents, Matthew and Mary Wagner.

Mary B. Winton

To Tracy L. Yeager, my husband, my soulmate, and support;
and to my boys, Jacob and Joshua, for putting
up with my hours on the computer; and I wouldn't be me without
thanking my dog, Xander, for being my constant companion.

Jennifer J. Yeager

MEET THE AUTHORS

LINDA E. MCCUISTION

Dr. Linda E. McCuistion received a Diploma of Nursing from the Lutheran Hospital School of Nursing in Fort Wayne, Indiana; Bachelor of Science in Nursing from William Carey College in Hattiesburg, Mississippi; Masters in Nursing from Louisiana State University Medical Center, New Orleans; and PhD in Curriculum and Instruction from the University of New Orleans. She was licensed as an Advanced Practice Nurse in Louisiana and has many years of nursing experience that include acute care and home health nursing. For 20 years, Linda was a Nursing Professor at University of Holy Cross in New Orleans, Louisiana. She received an Endowed Professorship Award in 2000 and 2003. Linda also worked as a nursing professor at South University, Richmond, Virginia.

Linda has served as a past president, vice president, and faculty advisor of the Sigma Theta Tau International Honor Society in Nursing, Xi Psi chapter-at-large. She is a past associate editor of the *NODNA Times,* a New Orleans District Nurses Association newsletter. She has been a member of Phi Delta Kappa and the American Society of Hypertension.

Linda was coordinator for the Graduate Plus internship program, a preceptorship program for new nursing graduates in the state of Louisiana. She has served as a legal nurse consultant; a member of a medical review panel; advisory board member, consultant, and reviewer of a software preparation company focused on the state licensure examination; advisory board member for a school for surgical technicians; and consultant to a local hospital to improve the quality of nursing care and assist acute care facilities in preparation for accreditation.

Linda was chosen as a "Great One-Hundred Nurse" by the New Orleans District Nurses Association in 1993. She is also listed in the 2005/2006 edition of the Empire Who's Who Executive and Professional Registry.

Linda has given numerous lectures and presentations regionally and nationally on a variety of nursing topics. She has published articles in nursing journals and has authored many chapters in several nursing textbooks, including *Pharmacotherapeutics: Clinical Decision Making in Nursing* (1999), *Saunders Manual of Medical-Surgical Nursing: A Guide for Clinical Decision Making* (2002), and *Saunders Nursing Survival Guide: Pathophysiology* (2007). She is author and coauthor of many chapters and coeditor of *Saunders Nursing Survival Guide: Pharmacology* (2007).

Linda enjoys cruises, the beach, and other travel. When at home, she enjoys family, friends, golf, crafts, reading, writing, and her King Charles Cavalier Spaniel, Prince.

KATHLEEN VULJOIN DIMAGGIO

Kathleen Vuljoin DiMaggio received her Bachelor of Science in Nursing from Our Lady of Holy Cross College of New Orleans and her Master of Science in Nursing from Loyola University of New Orleans, with a focus on Healthcare Systems Management. She completed a preceptorship in palliative care at Ochsner Foundation Hospital through Loyola University. She received Level I designation from the National Hospice and Palliative Care Organization in hospice management and development. She is certified with the Louisiana Department of Health and Hospitals Developmental Disabilities as a Registered Nurse Instructor in medication administration. Kathleen has more than 23 years of clinical nursing experience and more than 12 years of baccalaureate nursing education. Her professional practice experience includes medical-surgical nursing and home health and hospice nursing. She has experience in nursing management and has worked as director of nursing for a facility specializing in developmental disabilities. In addition, Kathleen has worked as director of nursing in home health and hospice care. She has worked in quality improvement, disease management, and case management.

Kathleen has served as a volunteer for Junior Achievement of New Orleans, has volunteered for a local hospice agency, and has served in the homeless ministry through her church.

Kathleen is a member of the American Nurses Association, Louisiana State Nurses Association, Academy of Medical-Surgical Nurses, Sigma Theta Tau International Honor Society of Nursing, and Alpha Sigma Nu Jesuit Honor Society.

Kathleen is a recipient of the 2011 and 2015 Endowed Professorship from Eminent Eye, Ear, Nose and Throat Hospital. She has received the Order of St. Louis Award through the Archdiocese of New Orleans and has also received the Florence Nightingale Society Award for Nursing. Kathleen received outstanding faculty of the year award in 2017 from the University of Holy Cross New Orleans. She received the distinction of Professor Emerita from University of Holy Cross New Orleans in May 2018.

Kathleen enjoys spending time with family and friends. She enjoys crocheting, quilting, cooking, and reading.

MARY B. WINTON

Dr. Mary B. Winton received her Associate Degree in Nursing from Tarleton State University in Stephenville, Texas, a member of the Texas A&M University System; her Bachelor and Master of Science in Nursing from the University of Texas at Arlington; and her PhD in Nursing from the University of Texas at Tyler. Additionally, she is board certified through the American Nurses Credentialing Center as an Acute Care Adult Nurse Practitioner. Mary has many years of hospital nursing experience in areas including critical care, emergency, and medical-surgical nursing as both a nurse and as a nursing supervisor. Additionally, she was employed with a hospitalist group as an Acute Care Nurse Practitioner for many years. She is currently an Associate Professor in the College of Health Sciences and Human Services, School of Nursing, at Tarleton State University. Mary has experience in teaching graduate-level pharmacology, pathophysiology, health assessment, and nursing informatics, and she has vast experience teaching at all levels of the undergraduate nursing program, including nursing pathophysiology, pharmacology, and health assessment.

Mary has served as faculty advisor for the Student Nurses Association at Tarleton. She has been a member of several organizations, including Sigma Theta Tau International Honor Society in Nursing, Tau Chi chapter; American Nurses Association/Texas Nurses Association; Critical Care Nursing Education; and Rural Nurse Organization. She is actively involved in various university, college, school, and departmental committees.

During her career as a nurse educator, Mary was the recipient of the Texas A&M Student Evaluation Teaching Excellence Award and the O.A. Grant Excellence in Teaching Award. She was also a recipient of the AACN 2020-2021 *Scholarship of Teaching and Learning Excellence Award*. She has also taught English as a Second Language at her church of membership.

Mary's research interests include health disparity among minorities, especially among Korean immigrants; student learning outcomes; and the use of technology in classrooms. She has presented at several conferences and has published on the health care of Korean immigrants.

During her spare time, Mary enjoys spending time with her husband, daughters, and grandchildren. She also enjoys traveling, reading, crocheting, and snow skiing.

JENNIFER J. YEAGER

Dr. Jennifer J. Yeager graduated from the University of Portland, Oregon, in 1987 with her Bachelor of Science in Nursing degree; she attended the university on an Air Force ROTC nursing scholarship. After graduation, she began her nursing career as an Air Force officer, assigned to Wilford Hall USAF Medical Center in San Antonio, Texas. The Air Force provided Jennifer with excellent experience as a transplant/nephrology nurse; after 6 years on active duty, she entered the civilian world as a transplant coordinator at Methodist Medical Center in Dallas, Texas. While there, Jennifer began her Master of Science in Nursing degree at the University of Texas at Arlington; she completed her degree as an Adult/Gerontological Nurse Practitioner with Educator Role in 1998. After completing ANCC certification in both specialty areas, she went to work in the Baylor Health Care System as a nurse practitioner in Long-Term Care and Elder House Calls.

Jennifer moved to Stephenville, Texas in 2007 and began teaching at Tarleton State University. She completed her PhD in Nursing at the University of Texas at Tyler in Fall 2013. She teaches a variety of courses, both graduate level and undergraduate.

Jennifer's research interests revolve around simulation; in 2021, in collaboration with co-workers in other disciplines, she published two journal articles related to pandemic simulation.

To relax, Jennifer enjoys spending time with her family, including multiple dogs. She is a strong advocate for dog rescue organizations and participates in Texas Transports with her husband, transporting shelter dogs to no-kill rescues within the state. Her passion for dogs extends to Animal Assisted Therapy. Xander, her American Staffordshire Terrier, is not only a rescue but also a certified therapy dog who joins her at Tarleton to work with nursing students to reduce anxiety before exams and simulations.

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IN RECOGNITION

Joyce LeFever Kee taught a pharmacology course to student nurses for 10 years from 1980 to 1990 at the University of Delaware. At the time, there were very few pharmacology texts available, and what was published was not appropriate for some BSN and ADN nursing programs. Daniel Ruth from W.B. Saunders approached Kee in 1990 to write a pharmacology book for nurses. With experience in teaching the subject, Kee developed the contents and format for a pharmacology text.

The chapter Drug Action: Pharmaceutic, Pharmacokinetics, and Pharmacodynamics Phases became the first chapter in the first edition. These drug phases appear both in the Prototype Drug Charts and within the contents in most of the current chapters. There are many drug tables Kee developed that have been updated by coauthors through the years. The important part that Kee established in the chapters were the five steps of the Nursing Process.

Dr. Evelyn R. Hayes joined Kee starting with the first edition. Hayes developed certain chapters and took the responsibility to work with contributors for the book such as the six chapters on Reproductive and Gender-Related Agents among others.

Linda McCuistion joined Kee and Hayes in 2005. McCuistion has updated many of Kee's chapters with new drugs and content.

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PREFACE

The eleventh edition of *Pharmacology: A Patient-Centered Nursing Process Approach* is written for nursing students who can benefit from presentation of the principles of pharmacology in a straightforward, student-friendly manner. It focuses on need-to-know content and helps students learn to administer drugs safely and eliminate medication errors through extensive practice of dosage calculations and evidence-based application of the nursing process.

ORGANIZATION

Pharmacology: A Patient-Centered Nursing Process Approach is organized into 18 sections and 58 chapters. **Section I** is an introduction to pharmacology and includes thoroughly updated chapters on drug action, the drug approval process, cultural and pharmacogenetic considerations, drug interactions, over-the-counter drugs, ethical considerations, pediatric and geriatric considerations, drugs for substance use disorder, complementary and alternative therapies, life span issues, patient collaboration in community settings, the nursing process, patient-centered care, and the role of the nurse in drug research. This section will introduce the Next Generation NCLEX (NGN) Clinical Judgment Measurement Model (CJMM). Its focus is to develop clinical reasoning and clinical judgment skills in students' decision making. This edition contains several unfolding and single episode case studies presented using the CJMM six cognitive skills and contrasts these skills with the Nursing Process.

Section II focuses on patient safety and quality in pharmacotherapy, medication administration, and it features a comprehensive review of drug dosage calculations for adults and children that is a unique strength of this book. This unit, tabbed for quick reference, includes Systems of Measurement With Conversion Factors, Calculation Methods: Enteral and Parenteral Drug Dosages, Calculation Methods: Drugs That Require Reconstitution, Calculation Methods: Insulin Dosages, and Calculation Methods: Intravenous Flow Rates. Five methods of dosage calculation are presented with color coding for easy identification: basic formula, ratio and proportion/fractional equation, dimensional analysis, body weight, and body surface area. Integral to the sections on dosage calculations are clinical practice problems that feature actual drug labels in full color, which provide extensive practice in real-world dosage calculations. With this wide array of practice problems in a variety of health care settings, this unit eliminates the need to purchase a separate dosage calculations book.

Section III addresses nutrition, fluids, and electrolytes with separate chapters that cover vitamin and mineral replacement, fluid and electrolyte replacement, and nutritional support.

Sections IV through XVIII make up the core of *Pharmacology: A Patient-Centered Nursing Process Approach* and cover the drug classifications that students must understand to practice effectively. Each drug family chapter includes a chapter outline, learning objectives, at least one prototype drug chart, a drug table, and an extensive nursing process section.

- The **prototype drug charts** are a unique tool that students can use to view the many facets of a prototype drug through the lens of the nursing process. Each prototype drug is one of the common drugs in its drug class. The charts include drug class, contraindications, dosage, drug-lab-food interactions, pharmacokinetics, pharmacodynamics, therapeutic effects/uses, side effects, and adverse reactions. With these charts, students can see how the steps of the nursing process correlate with these key aspects of drug information and therapy.
- The **drug tables** provide a quick reference to routes, dosages, uses, and key considerations for the most commonly prescribed medications for a given class. They list the drug's generic names, dosages, uses and considerations, and specific information on half-life and protein binding.
- The **Clinical Judgment [Nursing Process]** provide a convenient summary of related concepts for concept-based curricula, patient assessments, patient problems, plan of care, and outcomes. These sections also include cultural content, nursing interventions, suggestions for patient teaching, and relevant herbal information.

ADDITIONAL FEATURES

Throughout this edition, we have retained, enhanced, and added a variety of features that teach students the fundamental principles of pharmacology and the role of the nurse in drug therapy:

- **Review questions** at the end of each chapter help prepare students for the NCLEX® examination with its increasing emphasis on pharmacology; answers are provided in Appendix A at the end of the textbook.
- **Patient safety boxes** include information on medication safety, complementary and alternative therapies, and more.
- **Critical thinking case studies**, **critical thinking unfolding case studies, and critical thinking single episode case studies** have been added to several chapters in this edition. These case studies follow the new Next-Generation NCLEX® Exam Clinical Judgment Model and will challenge students in forming clinical judgment skills.
- **Complementary and alternative therapies** appear throughout the text to provide students with a quick reference to information on popular herbs and their side effects, drug interactions, and more.
- **Anatomy and physiology** is contained in all drug therapy chapters, including illustrated overviews of normal anatomy and physiology. These introductions give students the foundation for understanding how drugs work in various body systems.
- **High-alert drugs** () and **safety concerns** () are identified within the text with distinctive icons that make it easy to find crucial information.

TEACHING AND LEARNING RESOURCES

The eleventh edition of *Pharmacology: A Patient-Centered Nursing Process Approach* is the core of a complete teaching and learning package for nursing pharmacology. Additional components of this package include resources designed specifically for students, resources designed specifically for faculty members, and resources designed for both students and faculty.

FOR STUDENTS

A comprehensive *Study Guide,* available for purchase separately, provides thousands of study questions and answers, including clinically based situational practice problems, drug calculation problems and questions (many with actual drug labels), and case studies to help students master textbook content. Answers are provided at the end of the *Study Guide*.

A completely updated Evolve website (http://evolve.elsevier.com/McCuistion/pharmacology) provides additional resources for students, including the following:

- **Review questions for the NCLEX® Examination** organized by chapter
- **Downloadable key points** for content review on the go

- **Pharmacology animations** and **videos**
- **Unfolding case studies** with review questions

FOR FACULTY MEMBERS

The updated faculty Evolve website (http://evolve.elsevier.com/McCuistion/pharmacology) includes all of the student resources mentioned previously plus the following instructor-only resources:

- NEW! Additional Next-Generation NCLEX® pharmacology case studies.
- ***TEACH for Nurses*** **Lesson Plans** focus on the most important content from each chapter and provide innovative strategies for student engagement and learning. The lesson plans include strategies for integrating nursing curriculum standards (QSEN, concept-based learning, and BSN essentials), links to all relevant student and instructor resources, and an original instructor-only case study in each chapter.
- **ExamView Test Bank** features more than 1000 NCLEX® Examination–format questions that include alternate-item questions as well as rationales and page references for each question.
- **PowerPoint Collection** features customizable slides with images, integrated audience response system questions, and NCLEX-style questions.
- **Image Collection** provides approximately 125 full-color images from the book.

This textbook may be supplemented with the drug content found on government agency websites, which supply the latest information regarding changes to drug brand names.

It is our hope that *Pharmacology: A Patient-Centered Nursing Process Approach* and its comprehensive ancillary package will serve as a dynamic resource for teaching students the basic principles of pharmacology as well as their vital role in drug therapy.

Linda E. McCuistion
Kathleen Vuljoin DiMaggio
Mary B. Winton
Jennifer J. Yeager

ACKNOWLEDGMENTS

We wish to extend our sincere appreciation to the many professionals who assisted in the preparation of the eleventh edition of *Pharmacology: A Patient-Centered Nursing Process Approach* by reviewing chapters and offering suggestions.

We wish to especially thank Joyce LeFever Kee, who originated this pharmacology textbook, and her coauthor Evelyn R. Hayes, who worked tirelessly on many editions of this book.

We wish to thank the current contributors: Christina DiMaggio Boudreaux, Linda Laskowski-Jones, and Jared Robertson.

We wish to thank those who created and updated the previous established chapters: Margaret Barton-Burke, Joseph Boullata, Jacqueline Rosenjack Burchum, Katherine L. Byar, Michelle M. Byrne, Karen Carmody, Robin Webb Corbett, Sandy Elliott, Linda Goodwin, Janice Heinssen, Marilyn Herbert-Ashton, Judith W. Herrman, Kathleen J. Jones, Bettyrae Jordan, Robert J. Kizior, Paula R. Klemm, Anne E. Lara, Linda Laskowski-Jones, Ronald J. LeFever, Patricia S. Lincoln, Patricia O'Brien, Laura K. Williford Owens, Byron Peters, Lisa Ann Plowfield, Larry D. Purnell, Nancy C. Sharts-Hopko, Jane Purnell Taylor, Donald L. Taylor, Lynette M. Wachholz, Marcia Welsh, Gail Wilkes, and M. Linda Workman.

Of course, we are deeply indebted to the many patients and students we have had throughout our many years of professional nursing practice. From them we have learned many fine points about the role of therapeutic pharmacology in nursing practice.

Our deepest appreciation goes to pharmaceutical companies for use of their drug labels. Pharmaceutical companies that extended their courtesy to this book include the following:

- Abbott Laboratories
- AstraZeneca Pharmaceuticals
- Aventis
- Bayer Corporation
- Bristol-Myers Squibb (including Apothecon Laboratories and Mead Johnson Pharmaceuticals)
- DuPont/Merck Pharmaceuticals
- Eli Lilly and Company
- Elkins-Sinn, Inc.
- Glaxo-Wellcome
- Marion Merrell Dow, Inc.
- McNeill Laboratory, Inc.
- Merck and Co., Inc.
- Parke-Davis Co.
- Pfizer Inc.
- Rhone-Poulenc Rorer
- SmithKline Beecham Pharmaceutical
- Wyeth-Ayerst Laboratories

Thanks to Becton, Dickinson and Company for the syringe displays. Thanks to CareFusion Corporation for the photos of the infusion pumps.

Our sincere thanks to Elsevier, especially Yvonne Alexopoulos, Senior Content Strategist; Luke Held, Senior Content Development Manager; and Kate Mannix, Senior Project Manager, for their suggestions and wonderful assistance.

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1

Clinical Judgment Measurement Model (CJMM) and the Nursing Process

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OBJECTIVES

- Explain the primary change in the Next Generation NCLEX (NGN).
- Explain Concept and how it relates to patient care and the nursing process.
- Explain the steps of the nursing process and how each step relates to the CJMM.
- Define the six cognitive skills in the Clinical Judgment Measurement Model (CJMM).
- Develop a set of patient-centered outcomes.
- Discuss at least eight principles for health teaching related to drug therapy.
- Define the nurse's role as related to planning medication administration.

OUTLINE

In everyday practice, nurses have many important tasks, with drug administration at the top of their list. It is estimated that about 40% of the nurse's time is spent administering medication. Knowledge of medications is essential to patient safety. Nurses are often the first line of defense against drug errors in patient care. Federal, state, and local authorities issue regulations and guidelines for practice, and each state has a nurse practice act that defines the scope and function under which the nurse practices. Health care institutions also have policies that help nurses follow federal and state guidelines and regulations.

The National Council of State Boards of Nursing's (NCSBN) research has led to the development of the Next Generation NCLEX (NGN). The NGN is designed to measure new graduates' competence in clinical judgment. This chapter introduces the NCSBN's Clinical Judgment Measurement Model (CJMM) as it relates to the nursing process.

EXPLANATION OF TERMS

Nursing Process

The nursing process is used by nurses for the appropriate delivery of patient care. It is a systematic, rational method that addresses health needs and aids in developing a plan of care that includes drug administration. The nursing process supports the nurse in delivering prioritized patient care.

The National Council of State Boards of Nursing (NCSBN) defines the nursing process as "a scientific, clinical reasoning approach to client care." Much study by the NCSBN reveals that nurses use clinical judgment skills more than the nursing process. The steps in the nursing process include (1) assessment, (2) analysis, (3) planning, (4) intervention, and (5) evaluation (NCSBN 2018). Analysis includes both defining and ranking the patient's problems according to priority.

Patient Problems

Patient problems and needs are the basis for the patient plan of care. The problems presented in this chapter closely identify with the use of NANDA-1 language. However, nursing problems replace the use of nursing diagnoses. When using patient problem terminology, the language better defines nursing clinical practice. Patient problems are in the Analyze Cues (Interpret patient problems) and Prioritize Hypothesis (Rank patient problems by priority) in the Clinical Judgment Measurement Model. In the Nursing Process, patient problems are in the Analysis phase (see Box 1.1).

The Nursing Alliance For Quality Care (NAQC)

The Nursing Alliance for Quality Care (NAQC) is an organization that supports quality patient-centered health care. The NAQC in partnership with the American Nurses Association (ANA) has published guidelines that support the core principles of patient-centered quality care. These guidelines aim to foster the patient relationship as the cornerstone of patient safety and quality. The NAQC's mission is to advance the highest quality, safety, and value of consumer-centered health care for all individual patients, their families, and their communities. NAQC believes it is the nurse's role to cultivate successful patient and family engagement. Family engagement is an essential component in reducing drug errors. The nurse serves as a patient advocate by supporting the patient's right to practice informed decision making and by maintaining patient-centered engagement in the health care setting. These guidelines include nurses at all levels of education and across all health care settings. NAQC principles are fundamental to patient-centered practice and safety in pharmacotherapy.

BOX 1.1 Steps of the Clinical Judgment Measurement Model and the Nursing Process

Clinical Judgment Measurement Model	Nursing Process
Recognize Cues	Assessment
Analyze Cues	Analysis (Interpret problems)
Prioritize Hypothesis	Analysis (Rank problems)
Generate Solutions	Planning
Take Action	Interventions
Evaluate Outcomes	Evaluations

CLINICAL JUDGMENT [NURSING PROCESS]

The NCSBN defines clinical judgment as the observed outcome of critical thinking and decision making (NCSBN, 2018). This edition will offer students a variety of case studies related to pharmacology that encourage the use of clinical judgment skills based on the NCSBN's Clinical Judgment Measurement Model (CJMM; Fig. 1.1). The unfolding case studies are somewhat complex in the information presented and encourage the use of clinical reasoning and clinical judgment skills in the student as the questions are answered.

The student will use CJMM's six cognitive skills: (1) Recognize Cues, (2) Analyze Cues, (3) Prioritize Hypothesis, (4) Generate Solutions, (5) Take Action, and (6) Evaluate Outcomes (see Box 1.1, which compares the Clinical Judgment Measurement Model and the Nursing Process).

Concept

The focus of *concept* is on the patient-centered model of care instead of the disease-centered model of care. Concept influences the organization of patient information and the delivery of the patient's care using the nursing process according to the patient's problems. Nursing care

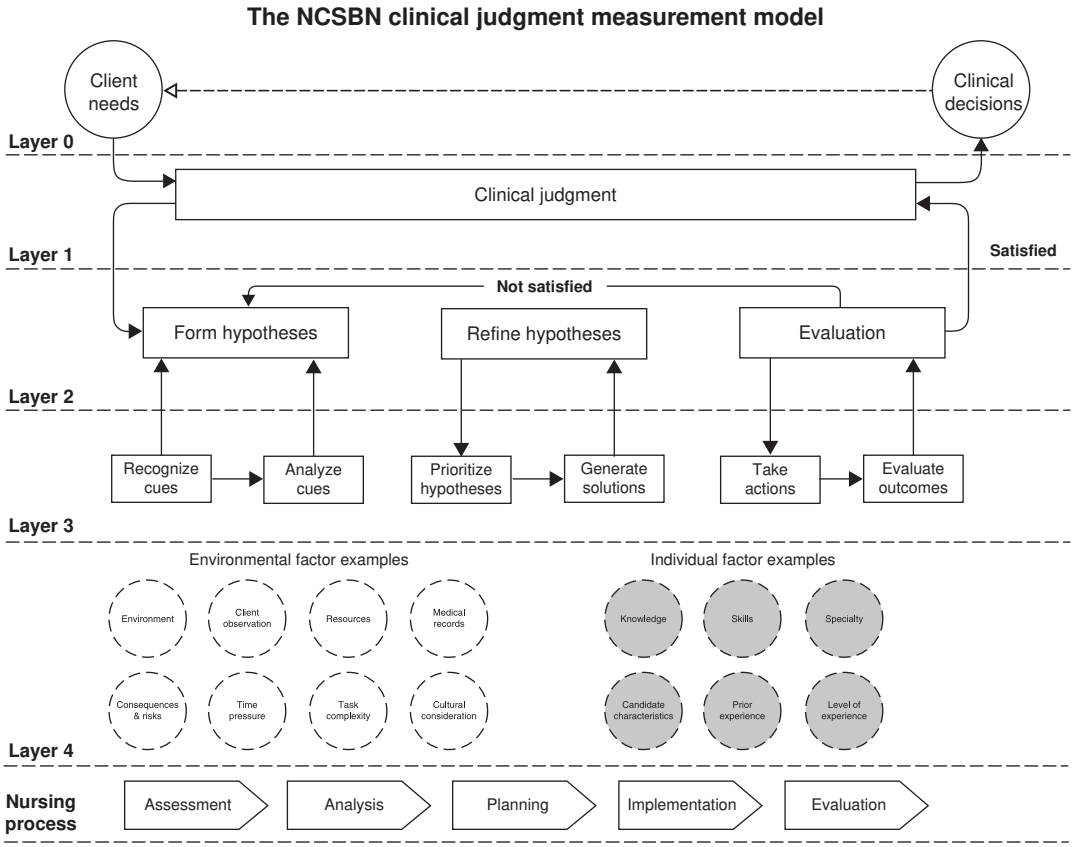


Fig. 1.1 NCSBN Clinical Judgment Model

plans using a nursing diagnosis organize information according to the patient's medical diagnosis.

The Concept centers its focus for nursing care around the reason the care is being provided to the patient. It is a more holistic view of the patient rather than the disease model. The term *Concept* includes health, illness, and health promotion of the patient. This involves preventive, primary, acute, and chronic health care for the ill patient.

Concepts are related to the patient's problems, the medications, or topics of care listed within the nursing process. A definition will immediately follow each concept (e.g., Concept: Safety—protecting the patient from possible injury by practicing safe medication administration.)

By focusing on the Concept, the nurse will provide patient education, restorative health needs, medication administration, and possibly emergency care. The nurse's attention is on promoting the patient's good health needs.

RECOGNIZE CUES [ASSESSMENT]

The nurse gathers cues (information) from the patient about their health and lifestyle practices. Cues are important facts about the patient that aid the nurse in making clinical care decisions. The nurse asks the patient direct questions about their illness. The data collected may be obtained from many different sources, including a systematic physical assessment of the patient's body systems and the medical record, which includes patient history, vital signs, and labs. With the patient's permission, information can be obtained from their family members. Also, other attending health care professionals can be consulted. The data collected are both subjective and objective data. Important cues are identified based on relevant (directly related) or irrelevant (unrelated) information concerning the patient's history, condition, and medical situation. It is vital to determine which data are most relevant to the patient's interventions and outcomes and of immediate concern for the delivery of priority care. This phase is paramount because the nurse will use the information gathered to form the basis of the patient's plan of care, which includes drug administration.

Subjective Data

Subjective data include information provided verbally by the patient, family members, friends, or other sources. The patient must verbalize subjective data, which are imperceptible by the nurse's senses. Subjective data are based on what patients or family members communicate to the nurse. The nurse may ask open-ended questions, allowing the patient to answer directly, such as, "Please tell me about your current medications." The nurse may help the patient explain or describe subjective data but must never speak for the patient. Subjective data comprise what the patient personally has to say about their medications, health problems, and lifestyle. Examples of pertinent information that the nurse can use to help solicit a response from the patient include the following:

- Inquire about the patient's current health history, including family history.
- Question whether or not the patient has problems swallowing (dysphagia).
- Have the patient verbalize signs and symptoms of their illness.
- Discuss the patient's current health concerns:
  - Knowledge of medications and side effects
  - Over-the-counter (OTC) remedies, nutritional supplements, herbal remedies, and contraceptives
  - Knowledge of side effects to report to the physician
  - Attitudes and beliefs about taking medications
  - Allergies
  - Financial barriers
  - Use of tobacco, alcohol, and caffeine
  - Cultural dietary barriers
  - The patient's home safety needs
  - Caregiver needs and support system

Enhancing the patient's adherence to their drug therapy regimen is an essential component of health teaching. The patient's attitudes and values about taking medication is an important consideration when determining readiness to learn. Attitudes and values should be considered when planning interventions to support the patient's decision to adopt healthy behaviors related to their medications. In addition, the patient's social support system should be emphasized. This special support system is unique to the individual and may be composed of persons who assist in preparing, organizing, and ordering medications. A support system can alert a patient to side effects, encourage actions that promote medication compliance, and notify the health care provider if a problem arises.

Objective Data

Objective data are what the nurse directly observes about the patient's health status. It involves collecting the patient's health information by using personal senses: seeing, hearing, smelling, and touching. Objective data collection provides additional information about the patient's symptoms and also targets the organs most likely to be affected by drug therapy. For example, if a drug is nephrotoxic, the patient's creatinine clearance should be assessed.

The following are examples of objective data assessed by the nurse concerning medication administration:

- Physical health assessment
- Laboratory and diagnostic test results
- Data from the physician's notes (i.e., health history)
- Measurement of vital signs
- The patient's body language

ANALYZE CUES [ANALYSIS] AND PRIORITZE HYPOTHESIS [ANALYSIS]

Analyze Cues and Prioritize Hypothesis are part of the Analysis phase of the Nursing Process. This involves identifying, organizing, and prioritizing the patient's problems from the data collected. Analyze Cues (facts) interprets the patient's problem(s). Prioritize Hypothesis organizes and ranks the problem(s).

Analyze Cues [Analysis]

Consider the cues (facts) in the context of the patient history and determine what kind of care the patient should receive. Ask yourself the following question, "How do these cues relate to the patient's condition or history?" Identify cues that support or contraindicate a problem or condition. Certain cues will be more concerning than others. This process will help identify potential complications and identify the patient's actual problems.

Prioritize Hypothesis [Analysis]

Once the cues (facts) are analyzed, the hypothesis (problem) is determined. The problems are organized, prioritized, and ranked according to acuity. There may be the need to collect additional patient assessment data.

When the cues show an abnormality, it serves as the defining characteristic of the patient's problem(s). Consider all possibilities about what is occurring in the patient's situation, including patient urgency and risk. Think about how the relevant cues relate to the patient's condition or history. Determine which cues are most likely serious and

why. Rank the problems according to priority (urgency, likelihood, risk, difficulty, and time). More than one applicable patient problem may be generated.

Patient Problem(s)

Some common patient problems related to drug therapy include:

- Abdominal pain
- Confusion
- Decreased adherence
- Need for health teaching
- Cognitive decline
- Nonadherence

Use of the patient problem(s) is beneficial to the patient because its focus is on the individual patient's care as related to a diagnosis derived from the patient's diagnostic illness. Its focus is patient-centered and not disease-oriented.

GENERATE SOLUTIONS [PLANNING]

This phase identifies expected outcomes and uses the patient's problem(s) to define a set of interventions to achieve the most desirable outcomes. The interventions are specific, evidence-based actions related to the expected outcomes. Consider which actual or potential actions should be avoided or contraindicated, as certain actions may be harmful to the patient in some situations.

Outcomes are patient centered, describe a specific activity, and include a time frame for achievement and reevaluation. Generate Solutions [Planning] includes the development of nursing interventions that assist the patient in meeting medication outcomes. To develop patient-centered expected outcomes, collaboration with the patient and/or family is necessary. Effective expected outcomes have the following qualities:

- The expected outcome is realistic, measurable, and includes reasonable deadlines.
- The expected outcome is acceptable to both the patient and nurse.
- The expected outcome is dependent on the patient's decision making ability.
- The expected outcome is shared with the health care team.
- The expected outcome identifies components for evaluation.

Examples of well-written comprehensive expected outcomes include the following:

- The patient will independently administer the prescribed dose of 4 units of regular insulin by the end of the fourth session of instruction.
- The patient will prepare a 3-day medication recording sheet that correctly reflects the prescribed medication schedule by the end of the second session of instruction.

TAKE ACTION [NURSING INTERVENTIONS]

This phase provides nursing education, drug administration, patient care, and other interventions necessary to accomplish the expected outcomes. The nurse decides which actions will address the highest priority of care. Actions may include, but are not limited to, additional assessment, patient health teaching, documentation, requesting prescriptions from the provider, implementation of nursing skills, consultation with health care team members, and drug administration.

Patient Teaching

It is important for the nurse to keep in mind factors that help promote patient learning: the patient's *readiness* to learn and investment in their learning. If the patient buys into wanting to practice good health principles, learning can be successful. The nurse and patient together must become fully engaged in the learning process.

Timing is another important factor. What is the best time for the patient to learn? Is the patient a morning or night person? People seem to learn best if the time between the learning and implementation is short. The environment should be conducive to learning with a temperature that is comfortable and an environment that is quiet. It is important for the nurse to recognize that certain barriers to learning exist. Pain is an obstacle, and the patient's teaching should be postponed until pain is relieved. Be mindful of language barriers. If the patient does not speak the same language as the nurse, an interpreter may be needed.

Patient teaching is essential to the patient's recovery. It allows the patient to become informed about his or her health problems and to participate in creating interventions that can lead to good health outcomes. It is within the scope and practice of the nurse to embrace patient education and to use health-teaching strategies.

Nurses have a primary role in teaching both patients and families about drug administration. It is important that teachings are tailored to the patient's educational level and that the patient trusts the nurse for learning to begin. With the patient's consent, it is always important to include a family member or friend in the teaching to provide support to the patient with reminders and encouragement; they can also detect possible side effects that may occur in the patient.

BOX 1.2 Patient Teaching Card

Name of drug: Acetaminophen 325–650 mg
Reason for taking the drug: Minor aches, pains, and fever
Dosage: One or two tablets as needed every 4 to 6 hours; maximum dose is 3250 mg daily unless under health care provider supervision, then 4 g daily may be used.
Time to take the drug: 8:00 a.m./2:00 p.m./8:00 p.m.
Possible side effects: Nausea, upper stomach pain, itching, loss of appetite, dark urine, and jaundice
Possible adverse effects: Overdosage can affect the liver and cause hepatotoxicity.
Notify health care provider: If side effects occur
Health care provider's telephone #: _____
Warning:

- *Never* take this medication with alcohol.
- If pregnant or nursing, notify the health care provider before taking the medication.
- Do not take this medication with other over-the-counter (OTC) drugs or supplements without notifying the health care provider.

General

The following are important principles to remember when teaching patients about their medications:

- Maintain the Health Insurance Portability and Accountability Act (HIPAA) when discussing the patient's medical records and personal health information with their family and friends.
- Prior to the teaching, assess the patient for health literacy skills such as the ability to read, write, listen, speak, communicate, and interact with others.
- Always allow the patient time to perform a repeat demonstration if taught a skill or a moment to teach-back the information learned. This confirms learning has taken place.
- Instruct the patient to take the drug as prescribed. Consistency in adhering to the prescribed drug regimen is important.
- Provide simple written instructions with the doctor and pharmacy names and telephone numbers.

- Advise the patient to notify their health care provider if any of the following occur:
  - The dose, frequency, or time of the drug is adjusted.
  - A female patient becomes pregnant.
  - An OTC medication or supplement is added.

Side Effects

Give the patient instructions that will help minimize any side effects (e.g., avoid direct sunlight with drugs that can cause photosensitivity or sunburn). Advise patients of any expected changes in the color of urine or stool, and counsel the patient who has dizziness caused by orthostatic hypotension to rise slowly from a sitting to a standing position.

Self-Administration

Perform an ongoing health literacy assessment of the patient's motor skills and abilities. Remember that modifications may be necessary to the teaching plan based on the assessment.

Instruct the patient according to the prescribed route: eye or nose instillation, subcutaneous injection, suppository, oral/mucosal (e.g., swish-and-swallow suspensions), and inhaled via a metered-dose inhaler with or without a spacer. Include a return demonstration in the instructions when appropriate.

The use of drug cards is a helpful teaching tool (see Box 1.2). Drug cards can be obtained from the health care provider, pharmacy, or drug manufacturer, or simply designed by the patient or caretaker. They are helpful components for teaching. Drug cards may include: the name of the drug; the reason for taking the drug; the drug dosage; times to take the drug; possible side effects; adverse effects; when to notify the care provider; and specific facts about what should or should not be done when taking the medication (e.g., take with food, do not crush tablets).

Diet

Advise the patient about foods to include in their diet and foods to avoid. Many foods interact with certain drugs. Depending on the nature of the interaction, certain foods have the ability to decrease drug absorption, increase the risk of drug toxicity, or create other problems that are important safety concerns.

Important Nursing Considerations

The nurse must keep in mind the patient's cultural needs to individualize the teaching plan. Begin by identifying your own cultural beliefs, practices, and values to keep them separate from those of the patient. If a language barrier exists, arrange for an interpreter who speaks the patient's language. Research shows that family members are not recommended as an effective interpreter because they may hinder communication. Ask the patient if there is something special you should know concerning his or her cultural needs.

Additional suggestions include the following:

- Space instruction over several sessions, and be flexible in the timing of medication teaching as desired by the patient.
- Allow time for patients to respond to questions. Ask open-ended questions, and have patients demonstrate their understanding of treatments rather than verbalizing them.
- Review community resources related to the patient's plan of care including medications.
- Collaborate with the patient and family and other health care staff and agencies to meet the patient's health care needs.
- Identify patients at risk for noncompliance with their drug regimen. Alert the health care provider and pharmacist so they can develop a plan to minimize the number of drugs and the number of times drugs are administered.
- Evaluate the patient's understanding of the medication regimen on a regular basis.

Fig. 1.2 Medication box and pill organizer. (Courtesy Apothecary Products, Inc., Burnsville, MN.)

BOX 1.3 Important Points for Patients and Families to Remember

- Medications should be taken as prescribed by your health care provider. If problems arise with the dose or timing or if side effects occur, contact your medical provider.
- If drugs are placed in a drug box, keep the original labeled containers.
- Keep all drugs out of the reach of children.
- Before using any over-the-counter (OTC) drugs, including vitamins and nutritional supplements, check with your health care provider. This includes the use of aspirin, ibuprofen, and laxatives. Consider consulting the pharmacist before buying or using a product.
- Bring all drugs with you when you visit the health care provider.
- Know the purpose of each medication and which side effect necessitates a call to the health care provider.
- Do not drink alcoholic beverages around the time you take your medications. Alcohol is absolutely contraindicated with certain medications, and it may alter the action and absorption of the medications.
- Be aware that smoking tobacco also can alter the absorption of some medications (e.g., theophylline-type drugs, antidepressants, pain medications). Consult your health care provider or pharmacist for specific information.

- Empower the patient to take responsibility for their drug management.
- General points to remember and tips for successful patient education are presented in Box 1.3.

Many people take multiple drugs simultaneously several times each day, which presents a challenge to patients, their families, and nurses. This complex activity of taking several drugs can be segmented into several simple tasks that include the following:

- Drug boxes (Fig. 1.2) obtained from a local pharmacy may be used to prepare and organize medications. These boxes have labeled compartments for each day of the week and several rows of compartments for drugs taken multiple times a day. The boxes sort the drugs according to the time of day each pill is to be taken. They can simplify the task of taking medications. However, it is important to remember the pill boxes must be filled correctly. A trusted relative or friend can always assist the patient when filling the boxes.
- Multidose pill packets are available from many local pharmacies. The pharmacy will package the patient's prescription medications into easy-to-open packages. Many pharmacies can provide a 30-day supply of the patient's prescription medications, individually packaged and labeled according to dose, date, and time at no extra cost.
- A recording sheet may be helpful. When the drug is administered, the patient or family member marks the sheet, which is designed to meet the patient's individual needs. For example, the time can

BOX 1.4 Medication Recording Sheet

Medication	Dosage Daily	DAYS OF WEEK S	M	T	W	Th	F	S
Captopril	12.5 mg							
Digoxin	0.25 mg							
Furosemide	40 mg							

be noted by the patient, or it can be entered beforehand, with the patient marking the designated time the dose is taken (Box 1.4).

- Alternatives to recording sheets are also available, and alarm reminder devices may be used.

Throughout the teaching plan, the nurse promotes patient independence (e.g., self-administering, safely storing, and ordering of the drug regimen). Always keep in mind patients' expected outcomes when teaching. Box 1.5 presents a checklist for health teaching in drug therapy.

BOX 1.5 Checklist for Health Teaching in Drug Therapy

- Assess the patient's health literacy skills to ensure that the patient has the capacity to obtain, process, and understand basic health information.
- Reinforce the importance of drug adherence.
- Always complete a health history and physical assessment on the patient.
- Assess all of the drugs on the patient's profile for possible drug interactions.
- Explain the reason the patient is taking the drug, the time it should be administered, and whether it should be taken with or without food.
- Review the side effects and adverse reactions, and make sure the patient has the doctor's telephone number and knows when to notify the health care provider or pharmacist.
- Distinguish whether the patient needs baseline or monthly laboratory work to monitor drug levels.
- Keep in mind that patient validation of learning may include a return demonstration of psychomotor skills (insulin administration).
- Show the patient how to record drug administration on a sheet of paper by indicating day and time drug is taken.
- Discuss the patient's financial resources and, if needed, consult a social worker for resources.
- Discuss the patient's support system such as family or friends as caregivers.
- Provide the patient with a list of community resources.

EVALUATE OUTCOMES [EVALUATION]

The nurse evaluates whether the patient's interventions and outcomes have been met and compares the patient's response with the expected outcomes. What signs point to improvement, decline, or appear unchanged in the patient? Determine whether the nursing interventions were effective, ineffective, or made no difference. If the interventions and expected outcomes are unmet, the nurse will revise the interventions and expected outcomes to ensure success. If the interventions and expected outcomes are met, the nurse will document the successful attainment in the patient's plan of care.

CRITICAL THINKING CASE STUDY

A 66-year-old man just arrived on the medical surgical unit after an emergency appendectomy. He is complaining of incisional pain, nausea, and headache. His blood pressure is 150/80, heart rate is 70 beats per minute, and his temperature is 100.8°F.

1. Identify the patient's highest priority assessment needs.
2. Formulate a nursing problem based on the patient's assessment data.
3. Name two nursing interventions that will achieve a positive outcome.
4. Evaluate the effectiveness of the interventions.
5. Have the expected outcomes been met?

REVIEW QUESTIONS

1. During a medication review session, a patient states, "I do not know why I am taking all of these pills." Based on this piece of subjective data, which problem will the nurse identify?
   - **a.** Pain
   - **b.** Knowledge
   - **c.** Fatigue
   - **d.** Anxiety
2. The nurse is developing a list of the patient's expected outcomes. Which is the best expected outcome for this patient?
   - **a.** The patient will self-administer albuterol by taking a deep breath before inhaling.
   - **b.** The patient will self-administer albuterol by the end of the second teaching session.
   - **c.** The patient will independently self-administer the prescribed dose of albuterol by the end of the second teaching session.
   - **d.** The patient will organize their medications according to the time each medication is due.
3. When developing an effective medication teaching plan, which component will the nurse identify as *most* essential?
   - **a.** Written instructions
   - **b.** The patient's readiness to learn
   - **c.** Use of colorful charts
   - **d.** A review of community resources
4. When developing an individualized medication teaching plan, which topics will the nurse include? (Select all that apply.)
   - **a.** Adherence to the prescribed drug regimen
   - **b.** Always using the prescribed drug route
   - **c.** Knowing adverse side effects to report to doctor
   - **d.** Always doubling the next dose if drug is missed
   - **e.** Telling the doctor when taking over-the-counter (OTC) supplements
5. The Nursing Alliance for Quality Care's main focus is for health care providers to strive for which goal?
   - **a.** Quality in medication administration
   - **b.** Confidentiality as determined by the patient
   - **c.** Development of a patient relationship/family engagement
   - **d.** Patient independence within the family of origin

6. Which teaching strategy is most likely to succeed in health teaching with the patient and family?
   a. Know the reason why each drug was ordered.
   b. Have patients learn the generic name of each pill.
   c. A repeat demonstration should follow the nurse's teaching.
   d. Have the patient identify the number and color of the pills.

7. Prioritize the steps of Clinical Judgment [Nursing Process]
   a. Generate Solutions [Planning]
   b. Analyze Cues [Analysis]
   c. Recognize Cues [Assessment]
   d. Prioritize Hypothesis [Analysis]
   e. Evaluate Outcomes [Evaluation]
   f. Take Action [Intervention]

2

Drug Development and Ethical Considerations

http://evolve.elsevier.com/McCuistion/pharmacology

OBJECTIVES

- Identify the three core ethical principles.
- Relate the core ethical principles that govern informed consent and risk-benefit ratio.
- Discuss the 2015 American Nurses Association Code of Ethics and its nine provisions.
- Describe the objectives of each phase of human clinical experimentation.
- Discuss federal legislation acts related to US Food and Drug Administration drug approvals.
- Explain the Canadian schedules for drugs sold in Canada.
- Describe the function of state nurse practice acts.
- Differentiate between chemical, generic, and brand names of drugs.
- Define "over the counter" as it relates to drugs.

OUTLINE

Approval of new drugs by the **US Food and Drug Administration (FDA)** has been steady since the early 2000s, reaching an all-time high in 2014 with the approval of 44 new drugs. To facilitate this increase, in 2004 the FDA established its **Critical Path Initiative**, a national strategy "to drive innovation in the scientific processes through which medical products are developed, evaluated, and manufactured." One focus of this initiative is on "improving the prevention, diagnosis, and treatment of rare and neglected disorders." Initiative successes include developing biomarkers and other scientific tools, streamlining clinical trials, and ensuring product safety.

The process of drug discovery and manufacturing takes 10 to 12 years, with a cost of more than $1 billion for each drug. Out of every 5000 to 10,000 compounds that begin preclinical testing, only one makes it through the FDA approval process. The steps of the process are shown in Fig. 2.1. Drug research and development is a complex process that is of particular interest and importance to professional nursing practice.

This chapter is devoted to a description of basic ethical principles that govern drug development and the nurse's role in this process.

CORE ETHICAL PRINCIPLES

Three core ethical principles are relevant to research involving human subjects: **respect for persons**, beneficence, and justice. Derived from the Belmont Report, the World Medical Association Declaration of Helsinki set out ethical principles for medical research that involves human subjects. These ethical principles are integral to the issues of informed consent and risk-benefit ratio in such research.

Respect for Persons

Patients should be treated as independent persons capable of making decisions in their own best interests. Patients with diminished decision-making capacity are entitled to protection. When making health care decisions, patients should be made aware of alternatives available to them as well as the consequences that stem from those alternatives. The patient's choice should be honored whenever possible. It is imperative that nurses recognize when patients are not capable of making decisions in their own best interest and are therefore entitled to protection. The nurse can assist with the determination of decision-making capacity through frequent assessment of the patient's cognitive status.

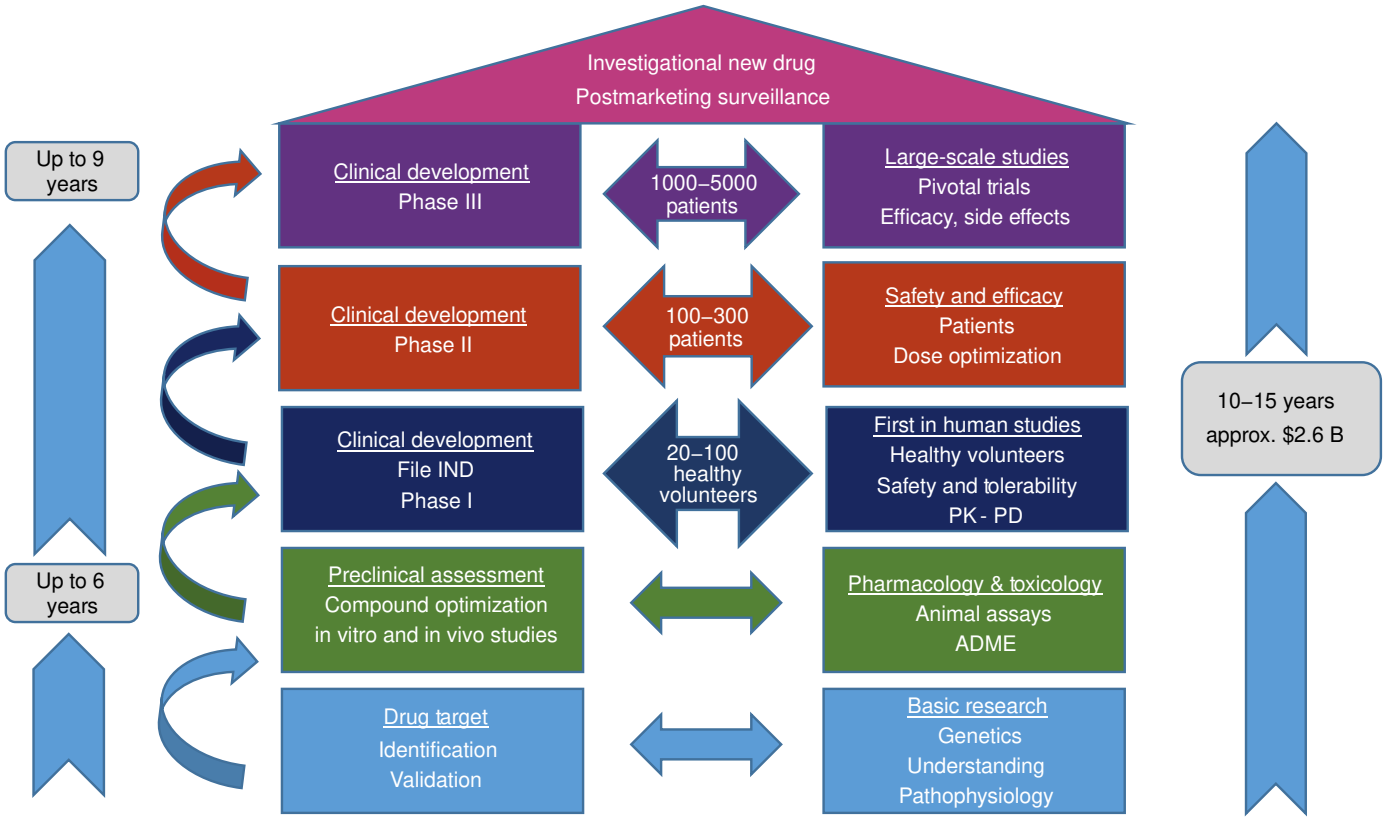


Fig. 2.1 The drug discovery and development process. *ADME,* Absorption, distribution, metabolism, and excretion; FDA, Food and Drug Administration; *IND,* investigational new drug; *PD,* pharmacodynamics; *PK,* pharmacokinetics. (From Wecker, L., Taylor, D. A., Theobald, R. J. [2019]. *Brody's human pharmacology* [6th ed.]. Philadelphia: Elsevier.)

Autonomy is an integral component of respect for persons. **Autonomy** is the right to self-determination. In health care settings, health care personnel must respect the patient's right to make decisions in their own best interest, even if the decision is not what the health care personnel want or think is best for the patient. Generally, patients can refuse any and all treatments (right of autonomy) except when the decision poses a threat to others—such as with tuberculosis, when taking medications is legally mandated. Autonomy is as relevant to the conduct of research as it is in health care decision making; patients have the right to refuse to participate in a research study and may withdraw from studies at any time without penalty.

Informed Consent

Informed consent has its roots in the 1947 Nuremberg Code. The two most relevant aspects of the Code are the right to be informed and that participation is voluntary, without coercion. If coercion is suspected, the nurse is obligated to report this suspicion promptly. Informed consent has dimensions beyond protection of the individual patient's choice:

- It is a mutual sharing of information, a process of communication.
- It expresses respect for the person.
- It gains the patient's active involvement in their care.
- It respects the patient's right to self-determination.

It is the role of the health care provider, *not* the nurse, to explain the study to the patient and what is expected of the patient and to respond to questions from the patient. When giving written consent, the patient must be alert and able to comprehend; consent forms should be written at or below the eighth-grade reading level, and words should be kept to fewer than three syllables.

Nurses are patient advocates. In collaboration with the health care provider and the pharmacist, the nurse must be knowledgeable about all aspects of a drug study—including all inclusion and exclusion criteria for participants (Box 2.1), study protocol, and study-related documentation—to promote participant safety and quality study results.

BOX 2.1 Sample Inclusion and Exclusion Criteria

Inclusion

- Persons between the ages of 18 and 65
- Persons weighing between 50 and 100 kg
- Persons on a stable dose (i.e., no dose change in the previous 3 months) of cardiac medications (e.g., anticoagulants, angiotensin-converting enzyme inhibitors [ACEIs], angiotensin II–receptor blockers [ARBs], beta blockers, and diuretics)
- Persons adhering to a no-added-salt diet

Exclusion

- Women who are pregnant or nursing
- Women of childbearing age who do not use oral contraceptives
- Persons with symptomatic cardiac disease, hepatic dysfunction, chronic kidney disease, neurologic disorders, or musculoskeletal disorders
- Persons with clinically significant abnormal laboratory values (chemistry and hematology)

Fig. 2.2 shows a sample of an informed consent form for a clinical drug trial, and Box 2.2 shows an informed consent checklist.

Beneficence

Beneficence is the duty to protect research subjects from harm. It involves ensuring the risks and possible benefits from participating in a research study are clearly defined and ensuring the benefits are greater than the risk.

Risk-Benefit Ratio

The **risk-benefit ratio** is one of the most complex problems faced by the researcher. All possible consequences of a clinical study must be analyzed and balanced against the inherent risks and the anticipated benefits. Physical, psychological, and social risks must be identified and weighed against the benefits. A requirement of the Department of Health and Human Services (DHHS) is that institutional review boards (IRBs) determine that risks to subjects be reasonable in relation to the anticipated benefits, if any, for subjects. No matter how noble the intentions, the calculation of risks and benefits by the researcher cannot be totally accurate or comprehensive.

Justice

Justice requires that the selection of research subjects be fair. Research must be conducted so that the distribution of benefits and burdens is equitable (i.e., research subjects reflect all social classes and racial and ethnic groups).

OBJECTIVES AND PHASES OF PHARMACEUTICAL RESEARCH

The FDA requires clinical research to follow the **Good Clinical Practice (GCP) Consolidated Guideline**, an international ethical and scientific quality standard for designing, conducting, monitoring, auditing, recording, analyzing, and reporting clinical research. It is the foundation of clinical trials that involve human subjects. Additional guidance and information sheets are available from the FDA on multiple topics related to clinical research.

Preclinical Trials

Before the implementation of clinical research, the FDA requires preclinical trials to determine a drug's toxic and pharmacologic effects through in vitro and in vivo animal testing in the laboratory. Through these trials, drug developers are able to determine **genotoxicity**, the ability of a compound to damage genetic information in a cell, in addition to drug absorption, distribution, metabolism, and excretion.

Human Clinical Experimentation

Historically, drug research was done only with Caucasian males, causing uncertainty as to the validity of research results for people of other ethnicities and for women and children. In 1993 Congress passed the National Institutes of Health (NIH) Revitalization Act, which helped establish guidelines to include women and minorities in clinical research. Additionally, the Best Pharmaceuticals for Children Act (BPCA) of 2002 and the Pediatric Research Equity Act (PREA) of 2003 encourage pharmaceutical companies to study their drugs in children.

Clinical experimentation in drug research and development encompasses four phases, each with its own objectives (see Fig. 2.1). A multidisciplinary team approach that includes nurses, physicians, pharmacologists, statisticians, and research associates is required to ensure safety and quality in all phases of clinical research. A brief description of each phase follows.

Phase I: Researchers test a new drug or treatment in a small group of people for the first time to evaluate its safety, determine a safe dosage range, and identify side effects.

Phase II: The drug or treatment is given to a larger group of people to see whether it is effective and to further evaluate its safety.

Phase III: The drug or treatment is given to large groups of people to confirm its effectiveness, monitor side effects, compare it with commonly used treatments, and collect information that will allow the drug or treatment to be used safely.

Phase IV: Studies are done after the drug or treatment has been marketed to gather information on the drug's effects in various populations and to assess any side effects associated with long-term use.

Pharmaceutical companies are eager to bring new drugs to market. To reduce delays in the FDA approval process, in 1992 Congress passed the Prescription Drug User Fee Act, which provided the FDA with funds to expedite the review process. As a result, the average drug approval time has decreased from 30 months to 12.

Clinical Research Study Design

An appropriate experimental design is important to answer questions about drug safety and efficacy. Studies are designed to determine the effect of the **independent variable** (treatment, such as with a drug) on the **dependent variable** (outcome, such as clinical effect). Intervening (extraneous) variables are factors that may interfere with study results, and these may include age, sex, weight, disease state, diet, and the subject's social environment. It is important to control for as many of the intervening variables as possible to increase study validity.

The *experimental group* in drug trials is the group that receives the drug being tested. The *control group* in drug trials may receive no drug; a different drug; a **placebo** (pharmacologically inert substance); or the same drug with a different dose, route, or frequency of administration.

AMERICAN NURSES ASSOCIATION CODE OF ETHICS

The **American Nurses Association (ANA) Code of Ethics** "was developed as a guide for carrying out nursing responsibilities in a manner consistent with quality in nursing care and the ethical obligations of the profession." It was first adopted in 1950 and most recently was revised with interpretive statements in 2015. The ANA Code of Ethics is founded on the principles first identified by Florence Nightingale, who believed that a nurse's ethical duty was first and foremost to care for the patient. The 2015 update addresses advances in nursing leadership, social policy and global health, and the challenges nurses face related to social media, electronic health records, and the nurse's expanded role in clinical research.

The Nurse's Role in Clinical Research

Nurses are at the forefront of clinical research. Regardless of the setting (inpatient or outpatient), nurses are likely to encounter patients eligible to participate, considering participation, or actively participating in clinical research. As such, nurses are responsible for both the safety of the patient and the integrity of the research protocol.

DRUG STANDARDS AND LEGISLATION

Drug Standards

The set of drug standards used in the United States is the United States Pharmacopeia (USP). The *United States Pharmacopeia and the National Formulary* (USP-NF), the authoritative source for drug standards (dosage, forms, drug substances, excipients, biologics, compounded preparations, and dietary supplements), is published annually. Experts in nursing, pharmaceutics, pharmacology, chemistry, and microbiology all contribute. Drugs included in the USP-NF have met high standards for therapeutic use, patient safety, quality, purity, strength, packaging safety, and dosage form. Drugs that meet these standards have the initials "USP" following their official name, denoting global recognition of high quality.

Sample Informed Consent Form for Randomized Clinical Trial of a Drug

Title of study: Comparison of a new drug [A] with an existing drug [B} used in treatment of disease X

Principal investigator: Dr. ABC

Institute: Department of Pediatrics, Aga Khan University

Introduction:

I am Dr. [SAK] from Department of Pediatrics, the Aga Khan University and doing a research on treatment of disease [X, for example malaria]. There is a new drug [A] which is being recommended for its treatment. I want to see if the new drug [A] is as good as or better than the commonly used drug [B] for the treatment of disease [malaria]. Since you are a patient of (or suffering from) disease [malaria], I would like to invite you to join this research study.

Background information

Disease X (Malaria) is a common disease in Pakistan, Asia and Africa, caused by a germ (parasite) spread by mosquito. It causes high grade fever. Some patients may have complications and even die. The commonly used drugs are losing their effectiveness and germs are getting resistant to it. A new drug known as [A] is supposed to be effective in treatment of disease (malaria) but there is not enough evidence that it is as good as other drugs used for treatment of disease (malaria).

Purpose of this research study

The purpose of study is to find out if the new drug is as good as or better than other drugs used for treatment of malaria in our population and; also to see if germs are not resistant to it.

Procedures

In this study, all patients aged 15 to 50 years of age, presenting at the clinic with fever for less than one week duration and having no other diagnosis will be registered and screened for malaria. For diagnosis of disease (malaria), one ml of blood will be taken from the patients and checked for presence of germs (malarial parasite). Those patients having positive test for the disease (malaria), will be included in the study. They will be divided randomly in to two groups by a computer draw. One group will get the new drug (A) and the other group will get the commonly used drug (B). Neither the doctor nor the patient will know which drug he/she is getting for treatment of his/her disease. A record will be kept for the duration of fever and other symptoms including any other side effect. Other necessary treatment will also be provided if needed.

Possible risks or benefits

No significant side effects have been reported for this new drug (A). However, some patients may feel nausea or may have vomiting. Drawing of blood may cause some discomfort or blue discoloration at the site of bleeding. Lowering of white blood cells and platelet is a common feature of the disease.

There is no direct financial or other benefit for the participant of the study. However, all the investigations will be done free of cost to the patients and; the drugs (A) or (B) will be provided free. Treatment of any side effect will also be provided free of cost. Sponsor of the study will bear the cost of drugs, investigations and treatment of side effects related to the study drugs.

Right of refusal to participate and withdrawal

You are free to choose to participate in the study. You may refuse to participate without any loss of benefit which you are otherwise entitled to. You child will receive the same standard care and treatment which is considered best for him irrespective of your decision to participate in the study. You may also withdraw any time from the study without any adverse effect on management of your child or any loss of benefit which you are otherwise entitled to. You may also refuse to answer some or all the questions if you don't feel comfortable with those questions.

Confidentiality

The information provided by you will remain confidential. Nobody except principal investigator will have an access to it. Your name and identity will also not be disclosed at any time. However the data may be seen by Ethical review committee and may be published in journal and elsewhere without giving your name or disclosing your identity.

Available Sources of Information

If you have any further questions you may contact Principal Investigator (Dr. SAK), department of pediatrics at Aga Khan University on following phone number 486xxxx

Fig. 2.2 Sample informed consent for a clinical trial of a drug. (From Sample Informed Consent for a Randomized Clinical Trial of a Drug. [n.d.] Aga Khan University. http://www.aku.edu/research/urc/ethicalreviewcommittee/sampleconsentforms/Pages/sampleconsentforms.aspx.)

1. AUTHORIZATION

I have read and understand this consent form, and I volunteer to participate in this research study. I understand that I will receive a copy of this form. I voluntarily choose to participate, but I understand that my consent does not take away any legal rights in the case of negligence or other legal fault of anyone who is involved in this study. I further understand that nothing in this consent form is intended to replace any applicable Federal, state, or local laws.

Participant's Name (Printed or Typed):
Date:

Participant's Signature or thumb impression:
Date:

Principal Investigator's Signature:
Date:

Signature of Person Obtaining Consent:
Date:

Fig. 2.2, cont'd

CLINICAL JUDGMENT [NURSING PROCESS]

Clinical Research

Concept: Safety
- Protection of the patient from potential or actual harm; it is a basic human need.

Recognize Cues [Assessment]
- Identify patients who are eligible to participate in or who are participating in clinical research.
- Assess response to the study agent and identify adverse events (an unfavorable or unintended sign, symptom, or disease that was not present at the time of study enrollment and is associated with the treatment or procedure).

Analyze Cues and Prioritize Hypothesis [Patient Problems]
- Need for health teaching
- Potential for decreased adherence

Generate Solutions [Planning]
- Have a process in place to identify persons who are eligible to participate in clinical research or to identify participants actively participating in clinical research studies.
- Have a process in place to facilitate education and informed consent of eligible study participants.
- Plan educational programming for staff who provide direct care to study participants.
- Plan participant care to ensure integrity and compliance with study protocol.

Take Action [Nursing Interventions]
- Support the process of informed consent in a culturally competent manner.
  - Provide an interpreter when necessary.
  - Provide enough time for the person to read the consent and ask questions.
  - Serve as a witness to informed consent.
- After reviewing the study protocol, administer study agent(s).
- Accurately document all participant care, assessment findings, and study agent administration.
- Accurately and safely collect biospecimens.
- Act as advocate, educator, and collaborator in the research process.
  - Ensure safe care.
  - Ensure integrity of study data.
  - Communicate clearly.

Evaluate Outcomes [Evaluation]
- Determine whether the potential participant understands what it means to participate in the study by asking open-ended questions.
- Monitor response to the study agent or other interventions.
- Determine whether participants understand how to take their study agents, what to do if they miss a dose, how to store the study agent, and when to call their health care provider.

The *International Pharmacopeia*, first published in 1951 by the World Health Organization (WHO), provides a basis for standards in strength and composition of drugs for use throughout the world. The book is published in English, Spanish, and French.

Federal Legislation

Federal legislation attempts to protect the public from drugs that are impure, toxic, ineffective, or not tested before public sale. The primary purpose of the legislation is to ensure safety. America's first law to regulate drugs was the Food and Drug Act of 1906, which prohibited the sale of misbranded and adulterated drugs but did not address drug effectiveness and safety.

1912: The Sherley Amendment

The Sherley Amendment prohibited false therapeutic claims on drug labels. It came about as a result of Mrs. Winslow's Soothing Syrup,

BOX 2.2 Informed Consent Checklist: Basic Elements

- A statement that the study involves research
- An explanation of the purposes of the research
- The expected duration of the subject's participation
- A description of the procedures to be followed
- Identification of any experimental procedures
- A description of any reasonably foreseeable risks or discomforts to the subject
- A description of any benefits to the subject or to others that may reasonably be expected from the research
- A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject
- A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained
- For research that involves more than minimal risk, an explanation as to whether any compensation will be paid and whether any medical treatments are available if injury occurs, and if so, what the treatments consist of or where further information may be obtained
- An explanation of whom to contact for answers to pertinent questions about the research and research subjects' rights and whom to contact in the event of a research-related injury to the subject
- A statement that participation is voluntary, refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled

From Office for Human Research Protections (OHRP). (2014). U.S. Department of Health & Human Services. Retrieved from http://www.hhs.gov/ohrp/policy/consentckls.html.

a product advertised to treat teething and colic, which contained morphine and led to the death of many infants. Under the Sherley Amendment, the government had to prove intent to defraud before a drug could be removed from the market.

1914: The Harrison Narcotics Tax Act

The Harrison Narcotics Tax Act required prescriptions for drugs that exceeded set narcotic limits. It also mandated increased record keeping by physicians and pharmacists.

1938: The Federal Food, Drug, and Cosmetic Act

The Federal Food, Drug, and Cosmetic Act of 1938 empowered the FDA to ensure a drug was safe before marketing. It is the FDA's responsibility to ensure that all drugs are tested for harmful effects; it also required that drugs be labeled with accurate information and have detailed literature in the drug packaging that explains adverse effects. The FDA can prevent the marketing of any drug it judges to be incompletely tested or dangerous. Only drugs considered safe by the FDA are approved for marketing.

1951: Durham-Humphrey Amendment

The Durham-Humphrey Amendment distinguished between drugs that could be sold with or without prescription by a licensed health care provider.

1962: Kefauver-Harris Amendment to the 1938 Act

The Kefauver-Harris Amendment resulted from the widely publicized thalidomide tragedy of the 1950s in which European patients who took the sedative-hypnotic thalidomide during the first trimester of pregnancy gave birth to infants with extreme limb deformities. The Kefauver-Harris amendment tightened controls on drug safety, especially experimental drugs, and required that adverse reactions and contraindications be labeled and included in the literature. The amendment also included provisions for the evaluation of testing methods used by manufacturers, the process for withdrawal of approved drugs when safety and effectiveness were in doubt, and the establishment of effectiveness of new drugs before marketing.

1965: Drug Abuse Control Amendments

Enacted in 1965, the Drug Abuse Control Amendments attempted to control the abuse of depressants, stimulants, and hallucinogens.

1970: The Comprehensive Drug Abuse Prevention and Control Act

In 1970 Congress passed the Comprehensive Drug Abuse Prevention and Control Act. This act, designed to remedy the escalating problem of drug abuse, included several provisions: (1) promotion of drug education and research into the prevention and treatment of drug dependence; (2) strengthening of enforcement authority; (3) establishment of treatment and rehabilitation facilities; and (4) designation of schedules, or categories, for controlled substances according to abuse liability.

Based on their abuse potential and acceptable medical use practices, **controlled substances** are categorized into five schedules, which are listed in Table 2.1. Schedule I drugs are not approved for medical use and have high abuse potential; schedule II through V drugs have acceptable medical use and decreasing potential for abuse leading to psychological and/or physiologic dependence.

Nurses are key to creating a culture of safety and accountability related to controlled substances. As such, nurses must:

- Verify orders before drug administration.
- Account for all controlled drugs.
- Maintain a controlled substance log that ensures all required information is documented accurately.
- Document all discarded or wasted medication; wastage must be witnessed by another nurse.
- Ensure timely documentation in the patient record after drug administration, including patient response to drug administration.
- Keep all controlled drugs in a locked storage area; keep narcotics under double lock. Be certain that only authorized persons have access to the keys, including keys for patient-controlled analgesia and epidural pumps. Medication may also be administered via an automated dispensing cabinet, with bioidentical identifiers used for access.
- The ANA recognizes the significant threat to patient safety and liability to health care organizations caused by nurse drug diversion and recommends that all states have a peer-to-peer assistance program for addicted nurses. Reporting is mandatory if suspected or known diversion occurs.

1983: The Orphan Drug Act

The Orphan Drug Act was designed to promote the development and manufacture of drugs used in the treatment of rare diseases (orphan drugs). The act's three primary incentives are (1) federal funding of grants and contracts to perform clinical trials of orphan products; (2) a 50% tax credit for costs of clinical testing; and (3) exclusive rights to market the drug for 7 years from the marketing approval date.

1994: Dietary Supplement Health and Education Act

The Dietary Supplement Health and Education Act established labeling requirements for dietary supplements and authorized the FDA to promote safe manufacturing practices. It classified dietary supplements as food.

TABLE 2.1 Schedule Categories of Controlled Substances

Schedule	Examples	Description
I	Some examples of drugs listed in Schedule I are heroin, lysergic acid diethylamide (LSD), *cannabis,* peyote, methaqualone, and methylenedioxymethamphetamine (MDMA).	Substances in this schedule have no currently accepted medical use in the United States, a lack of accepted safety for use under medical supervision, and a high potential for abuse.
II	Examples of Schedule II drugs include combination products with less than 15 milligrams of hydrocodone per dosage unit, cocaine, methamphetamine, methadone, hydromorphone, meperidine, oxycodone, fentanyl, dextroamphetamine, dextroamphetamine/amphetamine, and methylphenidate.	Substances in this schedule have a high potential for abuse that may lead to severe psychological or physical dependence.
III	Examples of Schedule III drugs include products containing less than 90 mg of codeine per dosage unit (acetaminophen with codeine), ketamine, anabolic steroids, and testosterone.	Substances in this schedule have a potential for abuse less than substances in Schedules I or II, and abuse may lead to moderate or low physical dependence or high psychological dependence.
IV	Examples of Schedule IV substances include alprazolam, carisoprodol, diazepam, lorazepam, zolpidem, and tramadol.	Substances in this schedule have a low potential for abuse relative to substances in Schedule III.
V	Examples of Schedule V drugs include cough preparations containing not more than 200 mg of codeine or per 100 mL (codeine/guaifenesin), diphenoxylate/atropine, difenoxin/atropine, and pregabalin.	Substances in this schedule have a low potential for abuse relative to substances listed in Schedule IV and consist primarily of preparations containing limited quantities of certain narcotics.

From United States Drug Enforcement Administration. (2018). Drug scheduling. Retrieved January 2, 2019 from https://www.dea.gov/drug-scheduling.

1996: Health Insurance Portability and Accountability Act

The Health Insurance Portability and Accountability Act (HIPAA) of 1996 protects health insurance coverage for workers who change or lose their jobs and sets the standard for the privacy of individually identifiable health information. The act provides patients more control over their health information, including boundaries on the use and release of health records.

1997: The Food and Drug Administration Modernization Act

The five provisions in the Food and Drug Administration Modernization Act are (1) review and use of new drugs is accelerated; (2) drugs can be tested in children before marketing; (3) clinical trial data are necessary for experimental drug use for serious or life-threatening health conditions; (4) drug companies are required to give information on off-label (non–FDA-approved) use of drugs and their costs; and (5) drug companies that plan to discontinue drugs must inform health professionals and patients at least 6 months before stopping drug production.

2002: Best Pharmaceuticals for Children Act

The BPCA gives manufacturers a 6-month extension of patents to evaluate drugs on the market for their safety and efficacy in children.

2003: Pediatric Research Equity Act

The Pediatric Research Equity Act authorizes the FDA to require that drug manufacturers test certain drugs and biologic products for their safety and effectiveness in children, noting that "children are not small adults." Additionally, studies that involve children must be conducted with the same drug and in the same disease process as adults.

2007: Food and Drug Administration Amendments Act

The Food and Drug Administration Amendments Act allows the FDA to do more comprehensive reviews of potential new drugs, mandates postmarketing safety studies, and affects the distribution of drugs found to be not as safe as premarket studies indicated.

2010: Patient Protection and Affordable Care Act

The Patient Protection and Affordable Care Act was signed into law in 2010 and became effective January 1, 2014. Essential provisions of the reform include (1) quality, affordable health care for all Americans; (2) improved quality and efficiency of health care; (3) prevention of chronic disease and improved public health; (4) improved access to innovative medical therapies; and (5) community living services and supports.

2012: Food and Drug Administration Safety and Innovation Act

The Food and Drug Administration Safety and Innovation Act was signed into law on July 9, 2012. It strengthens the FDA's ability to safeguard and advance public health by:

- Collecting fees from industry to fund reviews of drugs with the "breakthrough therapy" designation, medical devices, generic drugs, and biosimilar biologic products
- Expediting development of innovative, safe, and effective products
- Increasing stakeholder engagement in FDA processes
- Enhancing the safety of the global drug supply chain

NURSE PRACTICE ACTS

All states and territories have rules and regulations in place to provide guidance and govern nursing practice, which includes drug administration by nurses. Generally, nurses cannot prescribe or administer drugs without a health care provider's order. Practicing nurses should be knowledgeable about the nurse practice act in the state where they are licensed. (Information can be found through the National Council of State Boards of Nursing at www.ncsbn.org.) Nurses are responsible for knowing their state's law and administrative code. Nurses who administer a drug without a licensed health care provider's order are in violation of the Nurse Practice Act and can have their licenses revoked.

In a civil court, the nurse can be prosecuted for giving the wrong drug or dosage, omitting a drug dose, or giving the drug by the wrong route.

CANADIAN DRUG REGULATION

In Canada, before approval and becoming available to patients, drugs must be reviewed for safety, efficacy, and quality by the Health Products and Food Branch (HPFB) of Health Canada. Health Canada

TABLE 2.2 Canadian Controlled Drugs and Substances Schedule

Schedule	Examples	Description
I	Codeine, hydrocodone, oxycodone, coca, cocaine, levomethorphan, ketamine, sufentanil, methamphetamine, amphetamine, gamma hydroxybutyrate (GHB)	Opium poppy, coca leaves, phenylpiperidines, phenazepines, amidones, methadols, phenalkoxams, thiambutenes, moramides, morphinans, benzazocines, ampromides, benzimidazoles, phencyclidine, fentanyls, tilidine, methamphetamine, amphetamine, flunitrazepam, and GHB and its derivatives, alkaloids, and salts
II	Nabilone	Synthetic cannabinoid receptor type 1 agonists
III	Thirty-three compounds including methylphenidate, lysergic acid diethylamide (LSD), psilocybin, and mescaline	
IV	Twenty-six parent compounds including chlorphentermine, butorphanol, nalbuphine, meprobamate, and zolpidem	Barbiturates, thiobarbiturates, benzodiazepines, and their salts and derivatives; anabolic steroids and their derivatives
V		Propylhexedrine and any of its salts
VI	Class A includes 23 compounds such as ephedrine, ergotamine, and pseudoephedrine Class B includes six compounds such as acetone and sulfuric acid	Part 1 – Class A precursors Part 2 – Class B precursors Part 3 – Preparations and mixtures

For more detailed information, please see the Justice Laws Website at https://laws-lois.justice.gc.ca/eng/acts/c-38.8/page-14.html#h-95541.

is a federal department tasked with the mission of improving the quality of life of all Canadians. (Further information can be found at www.hc-sc.gc.ca.)

In 1996 the Canadian government passed the Controlled Drugs and Substances Act. This act broke controlled drugs and substances into eight schedules and two classes of precursors (Table 2.2). In 2012 the Safe Streets and Communities Act was passed in Canada, which reclassified amphetamines—including methylenedioxyamphetamine (MDA) and methylenedioxymethamphetamine (MDMA)—and also flunitrazepam and gamma hydroxybutyrate (GHB) from Schedule III to Schedule I drugs. This change imposed stiffer penalties for dealers and those in possession of the drugs.

INITIATIVES TO COMBAT DRUG COUNTERFEITING

Distribution of counterfeit drugs is a worldwide problem; it is estimated that more than 10% of all drugs available are counterfeit. Counterfeit drugs may contain the incorrect ingredients, insufficient amounts of active ingredients, or no active ingredients. Additionally, they may contain impurities and contaminants or may be distributed in fake packaging.

The most common drugs counterfeited are those used to treat erectile dysfunction, high cholesterol, hypertension, infections, cancer, and HIV/AIDS. The high cost of drugs, combined with the need for prescription drugs to treat chronic diseases—as well as the desire by consumers to misuse drugs (e.g., steroid-containing drugs for body building)—generates a constant demand easily filled by criminals via rogue Internet drug sites. The FDA and consumer groups are working on strategies to combat this problem, including tougher oversight of distributors, a rapid alert system, and better-informed consumers.

The role of the nurse is critical in consumer education. The nurse must advise patients to report any differences in taste or appearance of a drug or in its packaging. Patients should be alert to slight variations in packaging or labeling (e.g., color, package seal), note any unexpected side effects, and buy drugs from reputable sources. Reputable online pharmacies carry the designation of Verified Internet Pharmacy Practice Site (VIPPS; a list of VIPPS-verified pharmacies can be found at www.nabp.net) and display an approval seal. If any suspicion of counterfeit arises, the patient, family, or nurse should contact the FDA at www.fda.gov/Safety/MedWatch/HowToReport.

DRUG NAMES

Drugs have several names. The **chemical name** describes the drug's chemical structure. The **generic name** is the official, *nonproprietary* name for the drug; this name is not owned by any drug company and is universally accepted. Nearly 80% of all prescription drugs in the United States are ordered by generic name. The **brand (trade) name**, also known as the *proprietary* name, is chosen by the drug company and is usually a registered trademark. Drug companies market a compound using its brand name. For example, Lunesta is the (proprietary) brand name of a drug whose generic name is eszopiclone.

Throughout this text, only generic names for each drug will be used because many brand names may exist for a single generic name—for example, the generic drug ibuprofen carries the brand names Advil, Medipren, Motrin, and Nuprin. Generic names are given in lowercase letters, whereas brand names always begin with a capital letter. An example of a generic and brand-name drug listing is *furosemide (Lasix)*.

Generic drugs must be approved by the FDA before they can be marketed. If the generic drug is found to be *bioequivalent* to the brand-name drug, the generic drug is considered *therapeutically equivalent* and is given an "A" rating. If there is less than a 20% variance in drug absorption, distribution, metabolism, and excretion, a generic drug is considered *equivalent* to the brand-name drug.

A list of FDA-approved drug products can be found at www.accessdata.fda.gov/scripts/cder/drugsatfda. The FDA also publishes a list of approved generic drugs that are bioequivalent to brand-name drugs. Generic drugs have the same active ingredients as brand-name drugs but are usually less expensive because manufacturers do not have to do extensive testing; these drugs were clinically tested for safety and efficacy by the pharmaceutical company that first formulated the drug. However, all drugs have varying inert fillers, binders, and excipients used to shape tablets and control how fast or slow the drug is released in the body, and these factors may result in variations in drug bioavailability.

Health care providers and patients must exercise care when choosing generic drugs because of possible variations in their action or in the patient's response to them. To maintain stable drug levels, patients should be cautioned *not* to change generic drug manufacturers; this is particularly true when patients are prescribed phenytoin or warfarin. Nurses should check with the health care provider or the pharmacist

when generic drugs are prescribed. Health care providers must note on prescriptions whether the pharmacist may substitute the generic drug when the brand name is prescribed.

OVER-THE-COUNTER DRUGS

Although all drugs carry risk, **over-the-counter (OTC)** drugs have been found to be safe and appropriate for use without the direct supervision of a health care provider. They are available for purchase without a prescription in many retail locations. Other OTC drugs (e.g., pseudoephedrine, emergency contraception) are available with some restrictions and must be kept behind the pharmacy counter; before dispensing, patient age and identify are verified and education is provided.

More than $23 billion is spent annually on OTC drugs, which include vitamin supplements, cold remedies, analgesics, antacids, laxatives, antihistamines, sleep aids, nasal sprays, weight-control drugs, drugs for dermatitis and fungal infections, fluoride toothpaste, corn and callus removal products, and herbal products. Information related to OTC drugs available on the market can be found at http://www.drugs.com/otc.

In 2002 the FDA standardized OTC labeling to provide consumers with better information and to describe the benefits and risks associated with taking OTC drugs. It is an important nursing responsibility to ensure that patients are able to read and understand OTC labels. All OTC drugs must have labels that provide the following information in this specific order (Fig. 2.3).

- The product's active ingredients, including the amount in each dosage unit
- The purpose of the product
- The uses (indications) for the product
- Specific warnings, including when the product should not be used under any circumstances, substances or activities to avoid, side effects that could occur, and when it is appropriate to consult with a doctor or pharmacist
- Dosage instructions that include when, how, and how often to take the product
- The product's inactive ingredients and important information to help consumers avoid ingredients that may cause an allergic reaction

Nurses must be aware of OTC drugs and the implications of their use. OTC drugs provide both advantages and potential serious complications for the consumer. The nurse needs to emphasize that many of these drugs are potent and can cause moderate to severe side effects, especially when taken with other drugs. Additionally, many OTC drugs contain the same active ingredients, potentially leading to overdose. Self-diagnosis and self-prescribing OTC drugs may mask the seriousness of clinical conditions. See Box 2.3 for nursing considerations related to OTC drugs.

Many individuals routinely reach for aspirin, acetaminophen, and ibuprofen to relieve discomfort or pain without being aware of potential drug interactions and/or side effects. For example, ibuprofen can increase fluid retention, which can worsen heart failure; use of ibuprofen on a daily basis may decrease the effectiveness of antihypertensive drugs. Ibuprofen has also been linked with cardiovascular events, such as myocardial infarction and stroke; this risk increases with long-term use.

Acetaminophen has been associated with kidney disease, anemia and thrombocytopenia, myocardial infarction, stroke, and hypertension. Additionally, metabolism of the drug results in the development of toxic metabolites, which can cause liver damage. Patients may also develop allergic reactions (anaphylaxis) or potentially fatal skin reactions (Stevens-Johnson Syndrome [SJS] or toxic epidermal necrolysis [TEN]) when taking acetaminophen. Because of the potential for harm caused with high doses or long-term use, since 2011 the FDA has limited the dose of acetaminophen to 325 mg when packaged in combination with other drugs.

Some OTC drugs, such as cough medicine, are a combination product of two to four drugs. It is conceivable that there could be a drug-drug interaction with a cough medicine and one of the drugs prescribed by the patient's health care provider.

Patients with asthma should be aware that aspirin can trigger an acute asthma episode. Patients may be allergic to aspirin, or aspirin may act as a deregulator of leukotrienes. Aspirin is also not recommended for children with influenza symptoms or chickenpox because it has been associated with Reye syndrome. Patients with kidney disease should avoid aspirin, acetaminophen, and ibuprofen because these can further decrease kidney function, especially with long-term use. Also, patients taking moderate to high doses of aspirin, ibuprofen, or naproxen concurrently with an oral anticoagulant may be at increased risk for bleeding.

The previous examples are not all inclusive. Caution is advised before using any OTC preparation, including antacids, decongestants, and laxatives. Patients should check with their health care providers and read drug labels before taking OTC medications so they are aware of possible contraindications and adverse reactions.

The acronym *SAFER* is a mnemonic for the instructions that the FDA recommends before taking any medicine: **s**peak up, **a**sk questions, **f**ind the facts, **e**valuate your choices, and **r**ead labels.

DRUG RESOURCES

Many drug references are available, including nursing texts that identify related nursing implications and areas for health teaching. Some recommended resources follow.

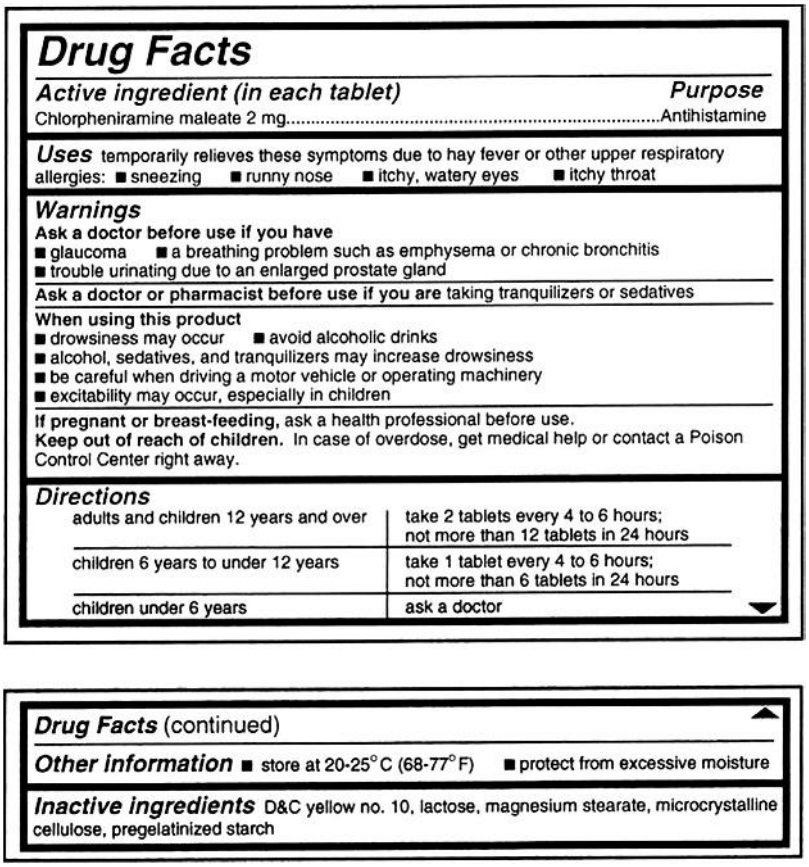
American Hospital Formulary Service (AHFS) Drug Information is published by the American Society of Health-System Pharmacists in Bethesda, Maryland. It provides accurate and complete drug information for both the health care provider and the consumer on nearly all prescription drugs marketed in the United States. This text contains drugs listed according to therapeutic drug classification. The information given for each drug includes chemistry and stability, pharmacologic actions, pharmacokinetics, uses, cautions, contraindications, acute toxicity, drug interactions, dosage and administration, and preparations.

This reference is updated yearly with monthly supplements that provide information on new drugs such as dosage forms and strengths, uses, and cautions. The text is unbiased. Drug information from the AHFS is available online or in print format.

United States Pharmacopeia—Drug Information (USP-DI) is available in most hospitals and pharmacies either online or in print format. It provides drug information for the health care provider, including pharmacology, precautions to consider, side effects and adverse effects, patient consultation, general dosing information, and dosage forms. The USP-DI also contains patient information presented in a way that is easily understood. The topics include administration of drugs, drug effects, indications, adverse reactions, dosage guidelines, and what to do for missed doses.

The *Medical Letter* on drugs and therapeutics is a nonprofit publication for physicians, nurse practitioners, and other health professionals. Each biweekly issue provides reviews of new FDA-approved drugs and comparisons of drugs available for common diseases.

Prescriber's Letter is a newsletter published monthly by the Therapeutic Research Center in Stockton, California. It provides



Drug Facts

Active ingredient (in each tablet) — **Purpose**
Chlorpheniramine maleate 2 mg ..... Antihistamine

Uses temporarily relieves these symptoms due to hay fever or other upper respiratory allergies: ■ sneezing ■ runny nose ■ itchy, watery eyes ■ itchy throat

Warnings
Ask a doctor before use if you have
■ glaucoma ■ a breathing problem such as emphysema or chronic bronchitis
■ trouble urinating due to an enlarged prostate gland

Ask a doctor or pharmacist before use if you are taking tranquilizers or sedatives

When using this product
■ drowsiness may occur ■ avoid alcoholic drinks
■ alcohol, sedatives, and tranquilizers may increase drowsiness
■ be careful when driving a motor vehicle or operating machinery
■ excitability may occur, especially in children

If pregnant or breast-feeding, ask a health professional before use.
Keep out of reach of children. In case of overdose, get medical help or contact a Poison Control Center right away.

Directions

adults and children 12 years and over	take 2 tablets every 4 to 6 hours; not more than 12 tablets in 24 hours
children 6 years to under 12 years	take 1 tablet every 4 to 6 hours; not more than 6 tablets in 24 hours
children under 6 years	ask a doctor

Drug Facts (continued)

Other information ■ store at 20-25°C (68-77°F) ■ protect from excessive moisture

Inactive ingredients D&C yellow no. 10, lactose, magnesium stearate, microcrystalline cellulose, pregelatinized starch

Fig. 2.3 Sample over-the-counter drug label. (From US Food and Drug Administration. [2014]. The current over-the-counter medicine label: Take a look. http://www.fda.gov/drugs/emergencypreparedness/bioterrorismanddrugpreparedness/ucm133411.htm.)

BOX 2.3 Nursing Considerations Related to Over-the-Counter Drugs

Nurses should advise patients of the following when over-the-counter (OTC) drugs are considered:

- Always read the instructions on the label.
- Do not take OTC medicines in higher dosages or for a longer time than the label states.
- If you do not get well, stop treating yourself and talk with a health care professional.
- Side effects from OTCs are relatively uncommon, but it is your job to know what side effects might result from the medicines you are taking.
- Because every person is different, your response to the medicine may be different than another person's response.
- OTC medicines often interact with other medicines and with food or alcohol, or they might have an effect on other health problems you may have.
- If you do not understand the label, check with the pharmacist.
- Do not take medicine if the package does not have a label on it.
- Throw away medicines that have expired (are older than the date on the package).
- Do not use medicine that belongs to a friend.
- Buy products that treat only the symptoms you have.
- If cost is an issue, generic OTC products may be cheaper than brandname items.
- Avoid buying these products online, outside of well-known Internet insurance company sites, because many OTC preparations sold through the Internet are counterfeit products. These may not be what you ordered and may be dangerous.

Parents should know the following special information about using OTCs for children:

- Parents should never guess about the amount of medicine to give a child. Half an adult dose may be too much or not enough to be effective. This is very true of medicines such as acetaminophen (Tylenol) or ibuprofen (Advil), in which repeated overdoses may lead to poisoning of the child, liver destruction, or coma.
- If the label says to take 2 teaspoons and the dosing cup is marked with ounces only, get another measuring device. Don't try to guess about how much should be given.
- Always follow the age limits listed. If the label says the product should not be given to a child younger than 2 years, do not give it.
- Always use the child-resistant cap, and relock the cap after use.
- Throw away old, discolored, or expired medicine or medicine that has lost its label instructions.
- Do not give medicine containing alcohol to children.

From Edmunds, M. W. (2016). *Introduction to clinical pharmacology* (8th ed). St. Louis, MO: Mosby.

concise updates and advice concerning new FDA-approved drugs, various uses of older drugs, and FDA warnings.

MedlinePlus is a service of the US National Library of Medicine. Available at www.nlm.nih.gov/medlineplus/druginformation.html, it offers extensive information on prescribed drugs, as well as herbs and supplements, indexed by generic and brand names.

A good source for OTC drug information is *The Handbook of Nonprescription Drugs,* published by the American Pharmacists Association in Washington, DC. This resource is available online and in text. The Internet can be another great resource, but only if credible websites are used.

CRITICAL THINKING CASE STUDY

A 53-year-old male is seen by his health care provider for chronic pain in his knees. He states the pain is a dull, constant ache in both knees that happens in the evenings after he's been working as a cashier all day.

1. It is important for the nurse to gather what information about the patient's medications?
2. The patient has taken ibuprofen for an extended period of time to control his pain. What risk does this over-the-counter (OTC) drug pose for him?
3. What patient education should the nurse provide concerning OTC drugs?
4. The patient is advised by his health care provider to stop taking ibuprofen and begin taking acetaminophen. Before leaving the office, he asks the nurse how he will be able to remember the possible side effects of this drug. The nurse tells him he can read the label on his bottle. What is the standardized order of information on OTC drug labels?

REVIEW QUESTIONS

1. The nurse in the clinical research setting is knowledgeable about ethical principles and protection of human subjects. What principle is demonstrated by ensuring the patient's right to self-determination?
   - **a.** Beneficence
   - **b.** Respect for persons
   - **c.** Justice
   - **d.** Informed consent
2. The research nurse is meeting with a patient and determines, based on the assessment, that the patient meets inclusion criteria for clinical research. The patient agrees to participate in the clinical trial. The nurse advises the patient that which member of the health care team has the responsibility to explain the study and respond to questions?
   - **a.** Registered nurse
   - **b.** Pharmacist
   - **c.** Research associate
   - **d.** Health care provider
3. The clinical research nurse knows that only a small proportion of drugs survive the research and development process. An appreciation of the process and associated costs grows when the nurse is aware that approximately one in how many potential drugs is approved by the US Food and Drug Administration?
   - **a.** 100
   - **b.** 1000
   - **c.** 10,000
   - **d.** 100,000
4. The nurse is interviewing a patient in a Phase I clinical trial. Which patient statement indicates an understanding of this trial phase?
   - **a.** I am doing this to be sure this drug is safe.
   - **b.** I am doing this to be sure this drug is effective.
   - **c.** I hope this drug is better than the current treatment.
   - **d.** I can be part of demonstrating a cure.
5. The foundation of clinical trials, Good Clinical Practice, is a helpful resource for nurses. The nurse is correct in choosing Good Clinical Practice as a reference for standards in which areas? (Select all that apply.)
   - **a.** Design
   - **b.** Monitoring and auditing
   - **c.** Analyses
   - **d.** Reporting
   - **e.** Outcomes evaluation
6. The nurse researcher reviews the proposed informed consent form for a future clinical trial. The nurse expects to find which in the document? (Select all that apply.)
   - **a.** Description of benefits and risks
   - **b.** Identification of related drugs, treatments, and techniques
   - **c.** Description of outcomes
   - **d.** Statement of compensation for participants, if any
   - **e.** Description of serious risks
7. The nurse knows that the patient should be informed about the risks and benefits related to clinical research. What ethical principle does this describe?
   - **a.** Respect for persons
   - **b.** Justice
   - **c.** Beneficence
   - **d.** Informed consent
8. The nurse is reviewing a patient's list of medications and notes that several have the highest abuse potential. According to US standards, the highest potential for abuse of drugs with accepted medical uses is found in drugs included in which schedule?
   - **a.** II
   - **b.** III
   - **c.** IV
   - **d.** V
9. The nurse is reviewing the drug approval process in the United States and learns that the Food and Drug Administration Modernization Act of 1997 contains which provisions? (Select all that apply.)
   - **a.** Review of new drugs is accelerated.
   - **b.** Drug companies must provide information on off-label use of drugs.
   - **c.** Privacy of individually identifiable health information must be protected.
   - **d.** Drug companies must offer advanced notice of plans to discontinue drugs.
   - **e.** Drug labels must describe side effects and adverse effects.
10. The patient has questions about counterfeit drugs. Which factors alert the patient or nurse that a drug is counterfeit or adulterated? (Select all that apply.)
    - **a.** Variations in packaging
    - **b.** Unexpected side effects
    - **c.** Different taste
    - **d.** Different chemical components
    - **e.** Different odor

11. The nurse knows the importance of administering the right medication to the patient and that drugs have many names. It is therefore most important that drugs be ordered by which name?
- **a.** Generic
- **b.** Brand
- **c.** Trade
- **d.** Chemical

12. What provisions from the Controlled Substances Act of 1970 were designed to remedy drug abuse?
- **a.** The act established treatment and rehabilitation facilities.
- **b.** The act tightened controls on experimental drugs.
- **c.** The act required clinical trial data on drugs.
- **d.** The act required drug companies to give information on off-label use of drugs.

3

Pharmacokinetics and Pharmacodynamics

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OBJECTIVES

- Differentiate the three phases of drug action.
- Describe the four processes of pharmacokinetics.
- Identify the four receptor families.
- Describe the influence of protein binding on drug bioavailability.
- Check drugs for half-life, percentage of protein binding, therapeutic index, and side effects in a drug reference book.
- Differentiate the four types of drug interactions.
- Explain the three mechanisms involved with drug-drug interactions.
- Describe the effects of drug-nutrient interactions.
- Explain the meaning of drug-induced photosensitivity.
- Describe the nursing implications of pharmacokinetics and pharmacodynamics.

OUTLINE

Once a drug is administered, it goes through two phases, the pharmacokinetic phase and the pharmacodynamic phase. The *pharmacokinetic phase,* or what the body does to the drug, describes the movement of the drug through the body. It is composed of four processes: (1) absorption, (2) distribution, (3) metabolism (biotransformation), and (4) excretion (elimination). The *pharmacodynamic phase,* or what the drug does to the body, involves receptor binding, postreceptor effects, and chemical reactions. A biologic or physiologic response results from the pharmacodynamic phase.

PHARMACOKINETICS

Pharmacokinetics is the process of drug movement throughout the body necessary to achieve drug action. The four processes are (1) absorption, (2) distribution, (3) metabolism (or biotransformation), and (4) excretion (or elimination).

Drug Absorption

Drug **absorption** is the movement of the drug into the bloodstream after administration. Approximately 80% of drugs are taken by mouth (enteral). For the body to use drugs taken by mouth, a drug in solid form (e.g., tablet or capsule) must disintegrate into small particles and combine with a liquid to form a solution, a process known as *dissolution* (drugs in liquid form are already in solution), to be absorbed from the gastrointestinal (GI) tract into the bloodstream. Unlike drugs taken by mouth, eyedrops, eardrops, nasal sprays, respiratory inhalants, transdermal drugs, sublingual drugs, and parenteral drugs do not pass through the GI tract.

Tablets are not 100% drug. Fillers and inert substances—such as simple syrup, vegetable gums, aromatic powder, honey, and various elixirs—called *excipients* are used in drug preparation to allow the drug to take on a particular size and shape and to enhance drug dissolution. Some excipients, such as the ions potassium (K^+) in penicillin potassium and sodium (Na^+) in penicillin sodium, increase the absorbability of the drug. Penicillin is poorly absorbed by the GI tract because of gastric acid. However, by adding potassium or sodium salts, penicillin can be absorbed.

Disintegration is the breakdown of an oral drug into smaller particles. The rate of dissolution is the time it takes the drug to disintegrate and dissolve to become available for the body to absorb it. Drugs in

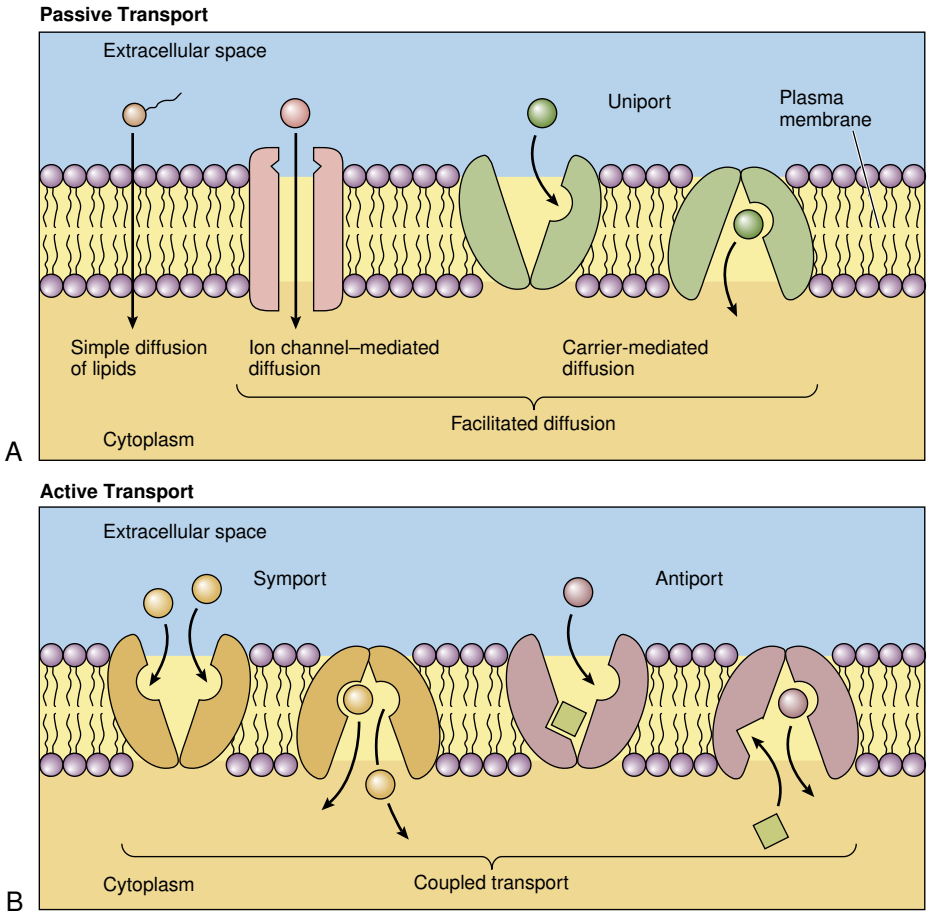

Fig. 3.1 Passive and active transport. *ATP,* Adenosine triphosphate. (From Gartner, L.P. [2017]. *Textbook of histology* [4th ed.]. St. Louis, MO: Elsevier.)

liquid form are more rapidly available for GI absorption than are solids. Generally, drugs are both disintegrated and absorbed faster in acidic fluids with a pH of 1 or 2 rather than in alkaline fluids (those with a pH greater than 7). Both the very young and older adults have less gastric acidity; therefore drug absorption is generally slower for those drugs absorbed primarily in the stomach.

Enteric-coated (EC) drugs resist disintegration in the gastric acid of the stomach, so disintegration does not occur until the drug reaches the alkaline environment of the small intestine. EC tablets can remain in the stomach for a long time; therefore their effect may be delayed in onset. EC tablets or capsules and sustained-release (beaded) capsules should not be crushed because crushing alters the place and time of absorption of the drug. Food in the GI tract may interfere with the dissolution of certain drugs. Some drugs irritate the gastric mucosa, so fluids or food may be necessary to dilute the drug concentration and provide protection.

Most oral drugs enter the bloodstream after absorption across the mucosal lining of the small intestine. The epithelial lining of the small intestine is covered with villi, fingerlike protrusions that increase the surface area available for absorption. Absorption is reduced if the villi are decreased in number because of disease, drug effect, or the removal of some or all of the small intestine.

Absorption across the mucosal lining of the small intestine occurs through passive transport, active transport, or pinocytosis. **Passive transport** occurs through two processes, diffusion and facilitated diffusion. In **diffusion,** drugs move across the cell membrane from an area of higher concentration to one of lower concentration. **Facilitated diffusion** relies on a carrier protein to move the drug from an area of higher concentration to an area of lower concentration. Passive transport does not require energy to move drugs across the membrane. **Active transport** requires a carrier, such as an enzyme or protein, to move the drug against a concentration gradient. Energy is required for active absorption (Fig. 3.1). **Pinocytosis** is a process by which cells carry a drug across their membranes by engulfing the drug particles in a vesicle.

The mucous membrane that lines the GI tract is composed of lipids (fat) and protein such that lipid-soluble drugs are able to pass rapidly through the mucous membrane. Water-soluble drugs need a carrier, either an enzyme or a protein, to pass through the mucous membrane. Large particles are able to pass through the mucous membrane if they are nonionized (have no positive or negative charge). Drugs that are lipid soluble and nonionized are absorbed faster than water-soluble and ionized drugs.

Blood flow, pain, stress, hunger, fasting, food, and pH affect drug absorption. Poor circulation to the stomach as a result of shock, vasoconstrictor drugs, or disease hampers absorption. Pain, stress, and foods that are solid, hot, or high in fat can slow gastric emptying time, so drugs remain in the stomach longer. Exercise can decrease gastric blood flow by shunting blood flow to peripheral muscles, thereby decreasing blood circulation to the GI tract.

Drugs given intramuscularly are absorbed faster in muscles that have increased blood flow (e.g., deltoid) than in those that do not (e.g., gluteus maximus). Subcutaneous tissue has decreased blood flow compared with muscle, so absorption is slower when drugs are given subcutaneously. However, drugs that are given subcutaneously have a more rapid and predictable rate of absorption than those given by mouth.

Drugs given rectally are absorbed slower than drugs administered by the oral route. Absorption is slower because the surface area in the rectum is smaller than the stomach, and it has no villi. Additionally, the

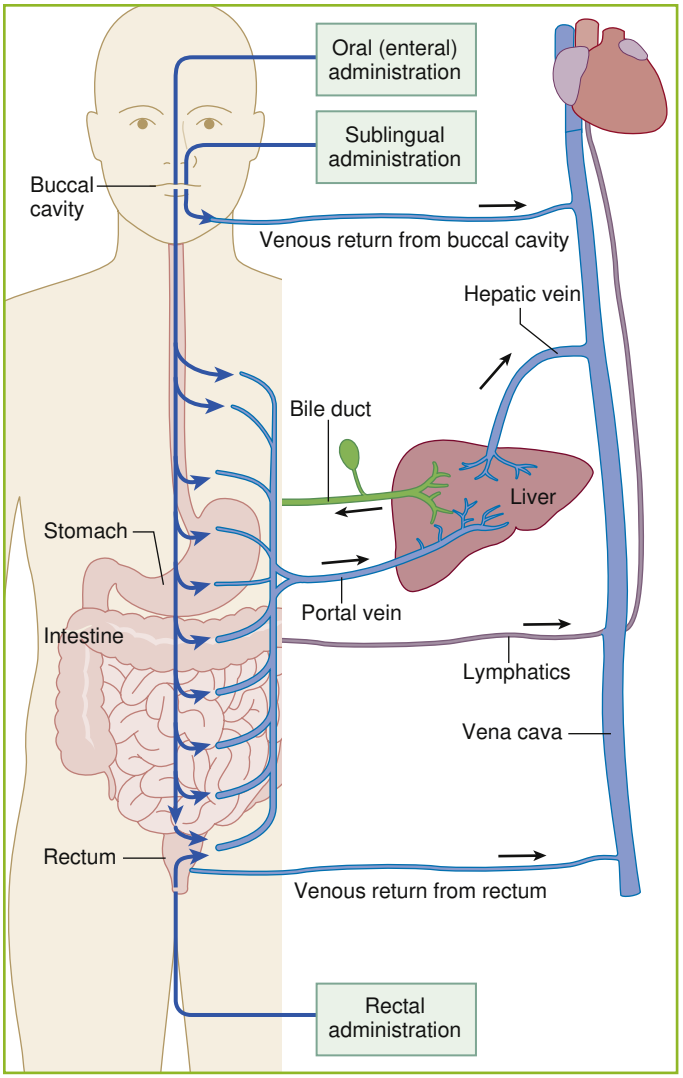

Fig. 3.2 First-pass metabolism. (From Kester, M. [2012]. *Elsevier's integrated review pharmacology* [2nd ed.]. St. Louis, MO: Elsevier.)

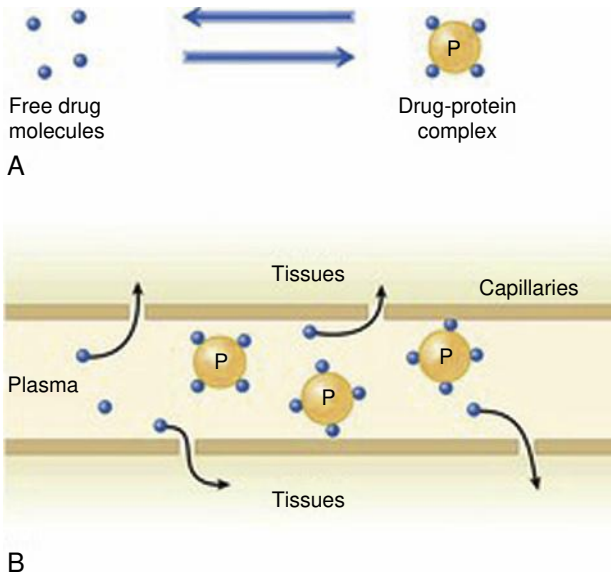

Fig. 3.3 Protein binding. *P,* Protein. (From Lilley, L. L., Rainform Collins, S., & Snyder, J. S. [2016]. *Pharmacology and the nursing process* [8th ed.]. St. Louis: Elsevier.)

composition of the suppository base (e.g., fatty bases or water-soluble bases) affects drug absorption.

After absorption of oral drugs from the GI tract, they pass from the intestinal lumen to the liver via the portal vein. In the liver, some drugs are metabolized to an inactive form and are excreted, thus reducing the amount of active drug available to exert a pharmacologic effect. This is referred to as the **first-pass effect** or **first-pass metabolism** (Fig. 3.2). Most oral drugs are affected to some degree by first-pass metabolism. Lidocaine and some nitroglycerins, for example, are not given orally because they have extensive first-pass metabolism and most of the drug is inactivated. Drugs that are delivered by other routes (intravenous [IV], intramuscular [IM], subcutaneous [SQ], nasal, sublingual, buccal) do not enter the portal circulation and are not subjected to first-pass metabolism.

Bioavailability refers to the percentage of administered drug available for activity. For orally administered drugs, bioavailability is affected by absorption and first-pass metabolism. The bioavailability of oral drugs is always less than 100% and varies based on the rate of first-pass metabolism (i.e., the bioavailability of rosuvastatin is 20%, whereas the bioavailability of digoxin ranges from 70% to 85%). The bioavailability of IV drugs is 100%.

Factors that alter bioavailability include the (1) drug form, such as tablet, capsule, sustained-release beads, liquid, transdermal patch, suppository, or inhalation; (2) route of administration (e.g., enteral, topical, or parenteral); (3) gastric mucosa and motility; (4) administration with food and other drugs; and (5) changes in liver metabolism caused by liver dysfunction or inadequate hepatic blood flow. A decrease in liver function or a decrease in hepatic blood flow can increase the bioavailability of a drug, but only if the drug is metabolized by the liver. Less drug is destroyed by hepatic metabolism in the presence of a liver disorder.

Drug Distribution

Distribution is the movement of the drug from the circulation to body tissues. Drug distribution is influenced by vascular permeability and permeability of cell membranes, regional blood flow and pH, cardiac output, tissue perfusion, the ability of the drug to bind tissue and plasma proteins (Fig. 3.3), and the drug's lipid solubility. Drugs are easily distributed in highly perfused organs such as the liver, heart, and kidney. Tissues with decreased perfusion, such as muscle, fat, and peripheral organs, result in decreased drug distribution.

Protein Binding

As drugs are distributed in the plasma, many bind with plasma proteins (albumin, lipoproteins, and alpha-1-acid-glycoprotein [AGP]). Acidic drugs such as aspirin and methotrexate and neutral drugs such as nortriptyline bind with albumin or lipoproteins; however, basic drugs (morphine, amantadine) bind to AGP. Drugs that are more than 90% bound to protein are known as *highly protein-bound drugs* (e.g., warfarin, glyburide, sertraline, furosemide, and diazepam); drugs that are less than 10% bound to protein are *weakly protein-bound drugs* (e.g., gentamicin, metformin, metoprolol, and lisinopril). The portion of the drug bound to protein is inactive because it is not available to interact with tissue receptors and therefore is unable to exert a pharmacologic effect. The portion that remains unbound is free, active drug. **Free drugs** are able to exit blood vessels and reach their site of action, causing a pharmacologic response.

When two highly protein-bound drugs are administered together, they compete for protein-binding sites, leading to an increase in free drug being released into the circulation. For example, if warfarin (99% protein bound) and furosemide (95% protein bound) were administered together, warfarin—the more highly bound drug—could displace furosemide from its binding site. In this situation, it is possible for drug accumulation to occur and for toxicity to result. Another factor that

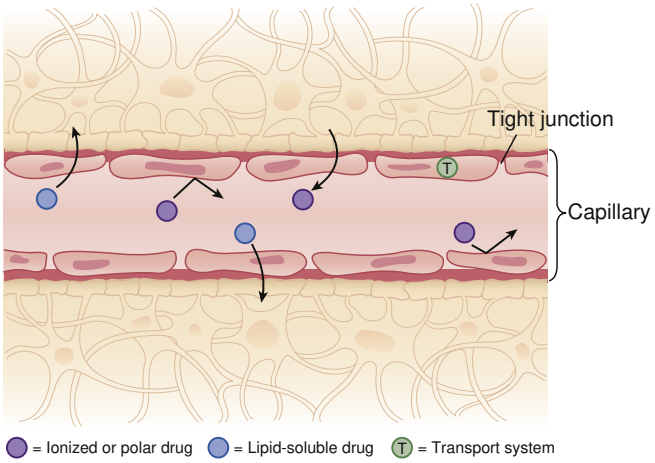

Fig. 3.4 Drug movement across the blood-brain barrier.

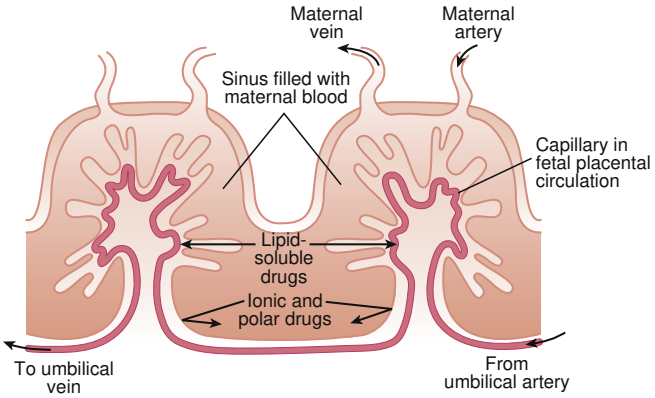

Fig. 3.5 Drug crossing the placenta.

may alter protein binding is low plasma protein levels, which potentially decrease the number of available binding sites and can lead to an increase in the amount of free drug available, resulting in drug accumulation and toxicity. Patients with liver or kidney disease and those who are malnourished may have significantly lower serum albumin levels. Additionally, older adults are more likely to have hypoalbuminemia, particularly if they have multiple chronic illnesses. With these factors in mind, it is important for nurses to understand the concept of protein binding and check their patients' protein and albumin levels when administering drugs.

Blood vessels in the brain have a special endothelial lining where the cells are pressed tightly together (*tight junctions*); this lining is referred to as the **blood-brain barrier (BBB)**. The BBB protects the brain from foreign substances, which includes about 98% of the drugs on the market. Some drugs that are highly lipid soluble and of low molecular weight (e.g., benzodiazepines) are able to cross the BBB through diffusion, and others cross via transport proteins. Water-soluble drugs (e.g., atenolol and penicillin) and drugs that are not bound to transport proteins (free drugs) are not able to cross the BBB, which makes it difficult for these drugs to reach the brain (Fig. 3.4).

During pregnancy, drugs can cross the placenta much as they do across other membranes, and this affects both the fetus and the mother (Fig. 3.5). Drugs taken during the first trimester can lead to spontaneous abortion. During the second trimester, drugs can lead to spontaneous abortion, teratogenesis, or other subtler defects. During the third trimester, drugs may alter fetal growth and development. The risk-benefit ratio should be considered before any drugs are given during pregnancy. During breastfeeding, drugs can pass into breast milk, which can affect the nursing infant. Nurses must teach women who breastfeed to consult their health care provider before taking any drug—whether over the counter (OTC) or prescribed—or any herb or supplement.

Drug Metabolism

Metabolism, or **biotransformation**, is the process by which the body chemically changes drugs into a form that can be excreted. The liver is the primary site of metabolism. Liver enzymes—collectively referred to as the *cytochrome P450 system,* or the *P450 system,* of drug-metabolizing enzymes—convert drugs to metabolites. A large percentage of drugs are lipid soluble; thus the liver metabolizes the lipid-soluble drug substance to a water-soluble substance for renal excretion. Liver diseases such as cirrhosis and hepatitis alter drug metabolism by inhibiting the drug-metabolizing enzymes in the liver. When the drug metabolism rate is decreased, excess drug accumulation can occur and can lead to toxicity.

Prodrugs

A **prodrug** is a compound that is metabolized into an active pharmacologic substance. Prodrugs are often designed to improve drug bioavailability; instead of administering a drug directly, a corresponding prodrug might be used instead to improve pharmacokinetics (absorption, distribution, metabolism, or excretion), decrease toxicity, or target a specific site of action. An example of a prodrug is codeine. Codeine itself has very little intrinsic activity at endogenous opioid receptors. However, drug-metabolizing enzymes in the liver convert codeine into morphine. Morphine, in turn, exhibits greater affinity for opioid receptors.

The drug **half-life** ($t_{1/2}$) is the time it takes for the amount of drug in the body to be reduced by half. The amount of drug administered, the amount of drug remaining in the body from previous doses, metabolism, and elimination affect the half-life of a drug. For example, with liver or kidney dysfunction, the half-life of the drug is prolonged, and less drug is metabolized and eliminated.

A drug goes through several half-lives before complete elimination occurs, and drug half-life is used to determine dosing interval. This is best understood with an example: ibuprofen has a half-life of about 2 hours. If a person takes 200 mg, in 2 hours, 50% of the drug will be gone, leaving 100 mg. Two hours later, another 50% of the drug will be gone, this time leaving 50 mg; in another 2 hours, 50% more will be gone, so only 25 mg will remain. This process continues such that 10 hours after 200 mg of ibuprofen has been taken, if no additional doses are administered, 6.25 mg of the drug remains.

Half-lives	% of Drug Eliminated From Body
1	50
2	75
3	87.5
4	93.75
5	96.875
6	98.474
7	99.25

Image reproduced with permission from Medscape, *Space out drug discontinuations prior to "drug holiday,"* 2000, available at https://www.medscape.com/viewarticle/413306.

By knowing the half-life, the time it takes for a drug to reach a **steady state** (plateau drug level) can be determined. A steady state occurs when the amount of drug being administered is the same as the amount of drug being eliminated; a steady state of drug concentration is necessary to achieve optimal therapeutic benefit. This takes about four half-lives, if the size of all doses is the same. For example, digoxin—which has a half-life of 36 hours with normal renal function—takes approximately 6 days to reach a steady-state concentration.

Loading Dose

However, in the case of drugs with long half-lives, it may not be acceptable to wait for a steady state to be achieved. Take, for example, the case of a person with seizures receiving phenytoin. The half-life of phenytoin is approximately 22 hours; if all doses of the drug were the same, a steady state would not be achieved for about 3½ days. By giving a large initial dose, known as a **loading dose**, that is significantly higher than maintenance dosing, therapeutic effects can be obtained while a steady state is reached. It bears repeating that the loading dose is larger than the dose needed to maintain the drug at steady state; it would produce toxic side effects if given in repeated doses. After the loading dose, maintenance dosing is begun; this is the dose needed to maintain drug concentration at steady state when given repeatedly at a consistent dose and constant dosing interval.

Drug Excretion

The main route of drug **excretion**, elimination of drugs from the body, is through the kidneys. Drugs are also excreted through bile, the lungs, saliva, sweat, and breast milk. The kidneys filter free drugs (in healthy kidneys, drugs bound to protein are not filtered), water-soluble drugs, and drugs that are unchanged. The lungs eliminate volatile drug substances, and products metabolize to carbon dioxide (CO_2) and water (H_2O).

The urine pH influences drug excretion. Normal urine pH varies from 4.6 to 8.0. Acidic urine promotes elimination of weak base drugs, and alkaline urine promotes elimination of weak acid drugs. Salicylic acid (aspirin), a weak acid, is excreted rapidly in alkaline urine. Treatment of salicylate toxicity includes IV administration of sodium bicarbonate to increase urine pH to 8.0 or higher (alkaline); maintaining alkaline urine promotes the excretion of salicylate at 18 times the normal rate.

Prerenal, intrarenal, and postrenal conditions affect drug excretion. Prerenal conditions, such as dehydration or hemorrhage, reduce blood flow to the kidney and result in decreased glomerular filtration. Intrarenal conditions, such as glomerulonephritis and chronic kidney disease (CKD), affect glomerular filtration and tubular secretion and reabsorption. Postrenal conditions that obstruct urine flow—such as prostatic hypertrophy, stones, and neurogenic bladder—adversely affect glomerular filtration. With any of these situations, drug accumulation may occur, resulting in adverse drug reactions.

Common tests used to determine renal function include creatinine and blood urea nitrogen (BUN). Creatinine is a metabolic by-product of muscle excreted by the kidneys; urea nitrogen is the metabolic breakdown product of protein metabolism. Based on National Kidney Foundation recommendations, the estimated glomerular filtration rate (eGFR) is now calculated as part of routine comprehensive metabolic panels (CMPs) and basic metabolic panels (BMPs). The eGFR is calculated using the person's creatinine level, age, body size, and sex. Decreased eGFR is expected in older adult and female patients because of their decreased muscle mass. It is important for nurses to know their patient's kidney function to ensure correct drug dosage.

PHARMACODYNAMICS

Pharmacodynamics is the study of the effects of drugs on the body. Drugs act within the body to mimic the actions of the body's own chemical messengers. Drug response can cause a primary or secondary physiologic effect or both. A drug's primary effect is the desirable response, and the secondary effect may be desirable or undesirable. An example of a drug with a primary and secondary effect is diphenhydramine, an antihistamine. The primary effect of diphenhydramine is to treat the symptoms of allergy; the secondary effect is a central nervous system (CNS) depression that causes drowsiness. The secondary effect is undesirable when the patient drives a car, but at bedtime it could be desirable because it causes mild sedation.

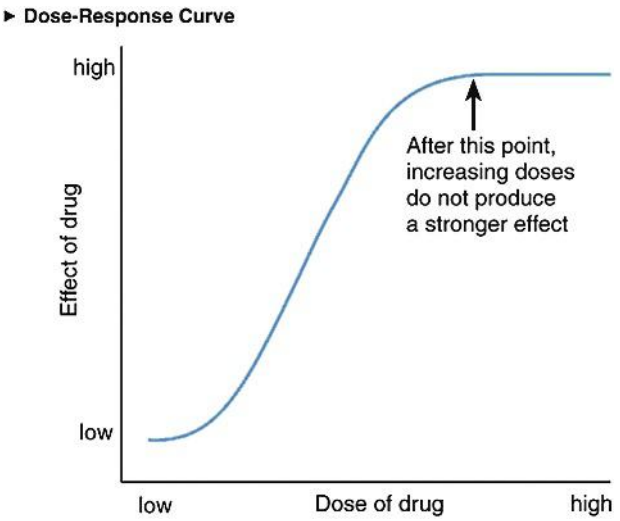

Fig. 3.6 Dose-response relationship. (From Carlson, N. R. [2010]. *Foundations of behavioral neuroscience* [8th ed.]. Upper Saddle River, NJ: Pearson.)

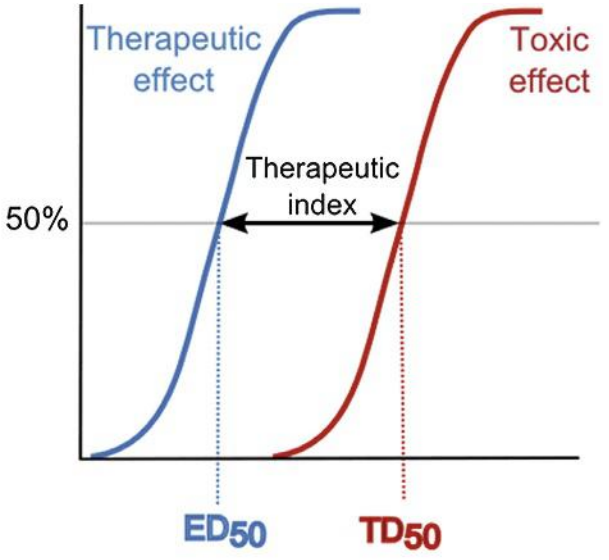

Fig. 3.7 The therapeutic index. The therapeutic index is the ratio between the toxic dose of a drug and the therapeutic dose of a drug. (From Guzman, F. [n.d.]. *Pharmacology corner.* Retrieved from http://pharmacologycorner.com/therapeutic-index/.)

Dose-Response Relationship

The **dose-response relationship** is the body's physiologic response to changes in drug concentration at the site of action. Two concepts further describe this relationship. **Potency** refers to the amount of drug needed to elicit a specific physiologic response to a drug. A drug with high potency, such as fentanyl, produces significant therapeutic responses at low concentrations; a drug with low potency, such as codeine, produces minimal therapeutic responses at low concentrations. The point at which increasing a drug's dosage no longer increases the desired therapeutic response is referred to as **maximal efficacy** (Fig. 3.6).

Closely related to dose-response and efficacy is the **therapeutic index (TI)**, which describes the relationship between the *therapeutic dose* of a drug (ED_{50}) and the *toxic dose* of a drug (TD_{50}). ED_{50} is the dose of a drug that produces a therapeutic response in 50% of the population; TD_{50} is the dose of a drug that produces a toxic response in 50% of the population. The therapeutic index is the difference between these two points (Fig. 3.7). If

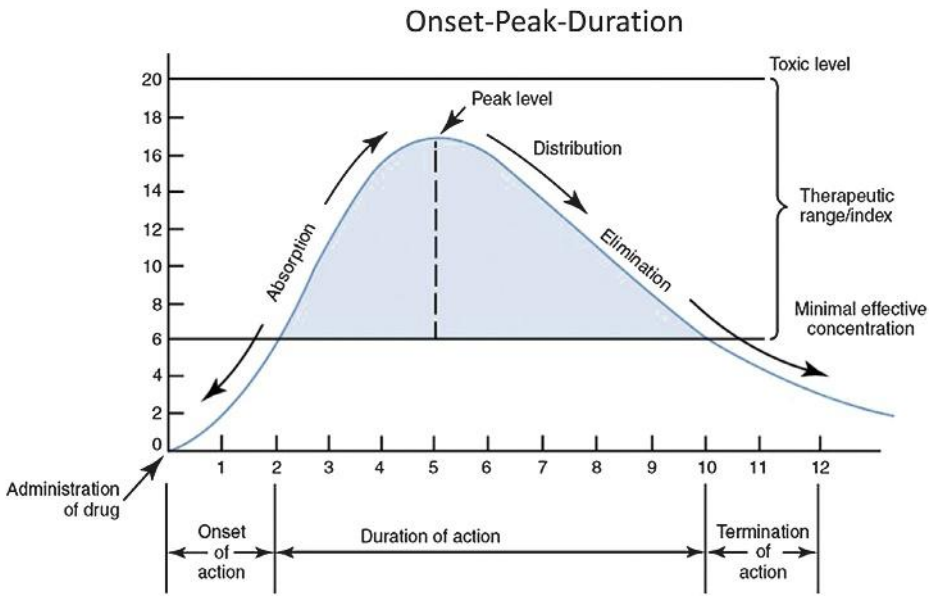

Fig. 3.8 Onset, peak, and duration of action. (From McKenry, L. M., Tessier, E., & Hogan, M. A. [2006]. *Mosby's pharmacology in nursing* [22nd ed.]. St. Louis, MO: Elsevier.)

the ED_{50} and TD_{50} are close, the drug is said to have a narrow therapeutic index. Drugs with a narrow therapeutic index—such as warfarin, digoxin, and phenytoin—require close monitoring to ensure patient safety. To be safe, plasma drug levels of drugs with a narrow therapeutic index must fall within the **therapeutic range** (also known as the therapeutic window). The therapeutic range is a range of doses that produce a therapeutic response without causing significant adverse effect in patients.

Onset, Peak, and Duration of Action

Other important aspects of pharmacodynamics to understand include a drug's onset, peak, and duration of action. **Onset** is the time it takes for a drug to reach the **minimum effective concentration** (MEC) after administration. The MEC is the minimum amount of drug required for drug effect. A drug's **peak** occurs when it reaches its highest concentration in the blood. **Duration of action** is the length of time the drug exerts a therapeutic effect. Fig. 3.8 illustrates the areas in which onset, peak, and duration of action occur.

It is necessary to understand this information in relation to drug administration. Some drugs produce effects in minutes, but others may take hours or days. If the drug plasma concentration decreases below the MEC, adequate drug dosing is not achieved; too high of a drug concentration can result in toxicity.

Therapeutic Drug Monitoring

Once a steady state has been achieved, drug concentration can be determined by measuring peak and trough drug levels. Peak and trough levels are requested for drugs that have a narrow therapeutic index and are considered toxic.

The **peak drug level** is the highest plasma concentration of drug at a specific time, and it indicates the rate of drug absorption. If the peak is too low, effective concentration has not been reached. If the drug is given orally, the peak time is usually 2 to 3 hours after drug administration. If the drug is given intravenously, the peak time is usually 30 to 60 minutes after the infusion is complete. If the drug is given intramuscularly, the peak time is usually 2 to 4 hours after injection. If a peak drug level is ordered, a blood sample should be drawn at the appropriate peak time based on the route of administration.

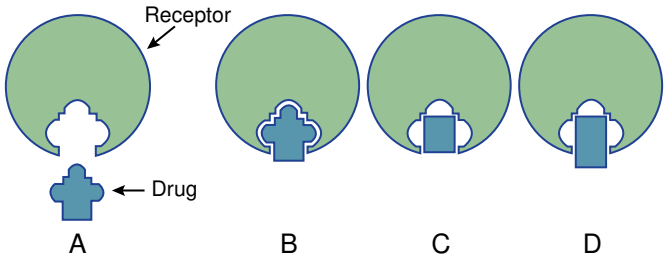

Fig. 3.9 (A) Drugs act by forming chemical bonds with specific receptor sites, similar to a key and lock. (B) The better the fit, the better the response. Drugs with complete attachment and response are called *agonists*. (C) Drugs that attach but do not elicit a response are called antagonists. (D) Drugs that attach and elicit a small response but also block other responses are called partial agonists. (From Clayton, B. D., & Willihnganz, M. J. [2017]. *Basic pharmacology for nurses* [17th ed.]. St. Louis, MO: Elsevier.)

Most drugs only require trough concentration levels to be drawn (the exception is aminoglycoside antibiotics, which require both peak and trough levels). The **trough drug level** is the lowest plasma concentration of a drug, and it measures the rate at which the drug is eliminated. Trough levels are drawn just before the next dose of drug regardless of route of administration.

Receptor Theory

Drugs act by binding to receptors. Binding of the drug may activate a receptor, producing a response, or it may inactivate a receptor, blocking a response. The activity of many drugs is determined by the ability of the drug to bind to a specific receptor. The better the drug fits at the receptor site, the more active the drug is. Drug-receptor interactions are similar to the fit of the right key in a lock. Fig. 3.9 illustrates drug-receptor binding.

Most **receptors**, which are protein in nature, are found on cell surface membranes or within the cell itself. Drug-binding sites are primarily on proteins, glycoproteins, proteolipids, and enzymes. The four receptor families (Fig. 3.10) include (1) cell membrane–embedded enzymes, (2) ligand-gated ion channels, (3) G protein–coupled receptor systems, and (4) transcription factors. The **ligand-binding domain** is the site on the receptor at which drugs bind.

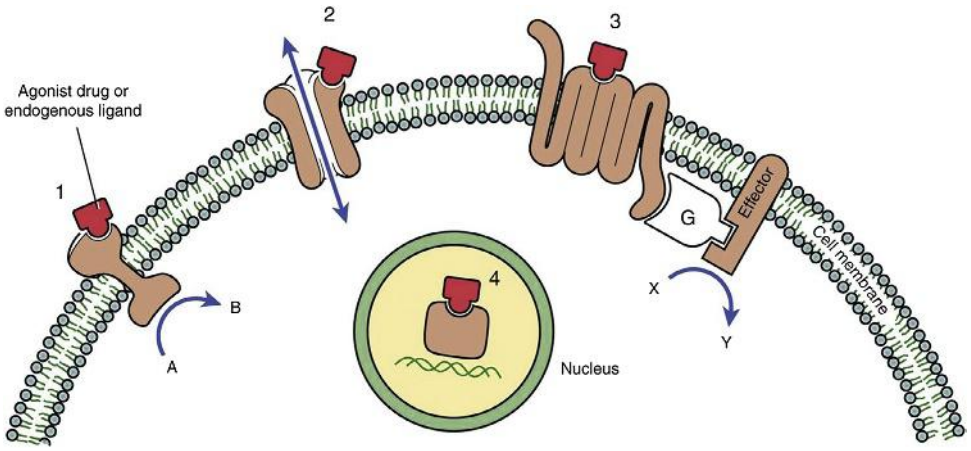

Fig. 3.10 **The four receptor families.** The four receptor families are (1) cell membrane–embedded enzymes, (2) ligand-gated ion channels, (3) G protein–coupled receptor systems, and (4) transcription factors. (From Burchum, J., & Rosenthal, L. [2016]. *Lehne's pharmacology for nursing care* [9th ed.]. St. Louis, MO: Elsevier.)

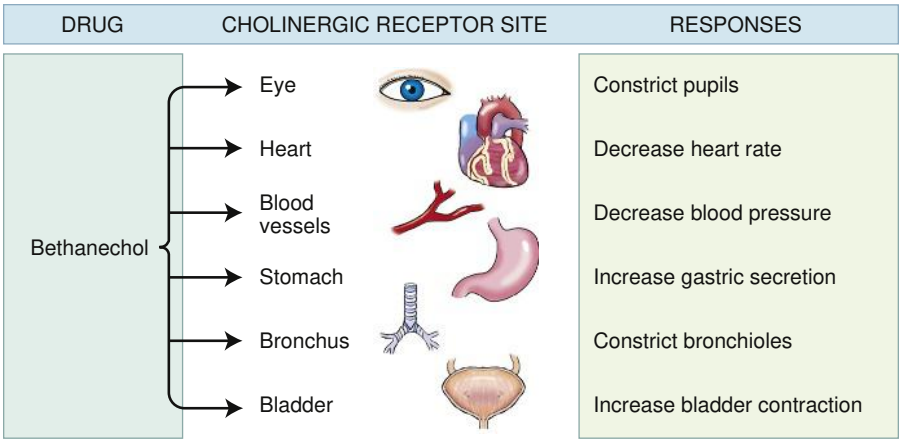

Fig. 3.11 Cholinergic receptors are located in the bladder, heart, blood vessels, stomach, bronchi, and eyes.

- *Cell membrane–embedded enzymes.* The ligand-binding domain for drug binding is on the cell surface. The drug activates the enzyme inside the cell, and a response is initiated.
- *Ligand-gated ion channels.* The channel crosses the cell membrane. When the channel opens, ions flow into and out of the cells. This primarily affects sodium and calcium ions.
- *G protein–coupled receptor systems.* The three components to this receptor response are (1) the receptor, (2) the G protein that binds with guanosine triphosphate (GTP), and (3) the effector, which is either an enzyme or an ion channel. The system works as follows:

$$\text{Drug} \xrightarrow{\text{Activates}} \text{Receptors} \xrightarrow{\text{Activates}} \text{G protein} \xrightarrow{\text{Activates}} \text{Effect}$$

- *Transcription factors.* Found in the cell nucleus on DNA, not on the surface. Activation of receptors through transcription factors regulates protein synthesis and is prolonged. With the first three receptor groups, activation of the receptors is rapid.

Agonists, Partial Agonists, and Antagonists

Drugs that activate receptors and produce a desired response are called **agonists**. **Partial agonists** are drugs that elicit only moderate activity when binding to receptors; partial agonists also prevent receptor activation by other drugs. Drugs that prevent receptor activation and block a response are called **antagonists**. Blocking receptor activation either increases or decreases cellular action, depending on the endogenous action of the chemical messenger that is blocked (see Fig. 3.9).

Nonspecific and Nonselective Drug Effects

Many agonists and antagonists lack specific and selective effects. Receptors produce a variety of physiologic responses, depending on where the receptor is located. Cholinergic receptors are located in the bladder, heart, blood vessels, stomach, bronchi, and eyes. A drug that stimulates or blocks the cholinergic receptors affects all anatomic sites. Drugs that affect multiple receptor sites are considered **nonspecific**. For example, bethanechol may be prescribed for postoperative urinary retention to increase bladder contraction. This drug stimulates cholinergic receptors located in the bladder, and urination occurs by strengthening bladder contraction. However, because bethanechol is nonspecific, other cholinergic sites are also affected; the heart rate decreases, blood pressure decreases, gastric acid secretion increases, the bronchioles constrict, and the pupils of the eye constrict (Fig. 3.11). These other effects may be either desirable or harmful.

Some drugs affect multiple receptors, and these are considered **nonselective** drugs. For example, epinephrine, which is used for treatment of anaphylaxis or severe asthma exacerbations, acts on the alpha$_1$, beta$_1$, and beta$_2$ receptors (Fig. 3.12), affecting multiple body systems.

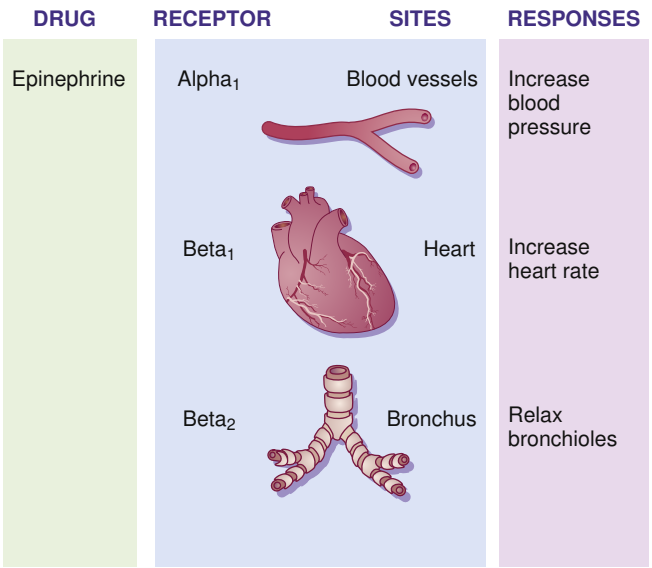

Fig. 3.12 Epinephrine affects three different receptors: alpha$_1$, beta$_1$, and beta$_2$.

Mechanisms of Drug Action

Mechanisms of drug action include (1) stimulation, (2) depression, (3) irritation, (4) replacement, (5) cytotoxic action, (6) antimicrobial action, and (7) modification of immune status. A drug that stimulates enhances intrinsic activity (e.g., adrenergic drugs that increase heart rate, sweating, and respiratory rate during fight-or-flight response). Depressant drugs decrease neural activity and bodily functions (e.g., barbiturates and opiates). Drugs that irritate have a noxious effect, such as astringents. Replacement drugs such as insulins, thyroid drugs, and hormones replace essential body compounds. Cytotoxic drugs selectively kill invading parasites or cancers. Antimicrobial drugs prevent, inhibit, or kill infectious organisms. Drugs that modify immune status modify, enhance, or depress the immune system (e.g., interferons and methotrexate).

Side Effects, Adverse Drug Reactions, and Drug Toxicity

Side effects are secondary effects of drug therapy. All drugs have side effects. Even with correct drug dosage, side effects occur that can be predictable and range from inconvenient to severe or life-threatening. In some instances, the side effects may be desirable (e.g., using diphenhydramine at bedtime, when its side effect of drowsiness is beneficial). Chronic illness, age, weight, sex, and ethnicity all play a part in drug side effects.

It is important to know that the occurrence of side effects is one of the primary reasons patients stop taking their prescribed medications. An important role of the nurse includes teaching patients about a drug's side effects and encouraging them to report side effects. Many can be managed with dosage adjustments, changing to a different drug in the same class, or implementing other interventions.

Adverse drug reactions (ADRs) are unintentional, unexpected reactions to drug therapy that occur at normal drug dosages. The reactions may be mild to severe and include anaphylaxis (cardiovascular collapse). Adverse drug reactions are always undesirable and must be reported and documented because they represent variances from planned therapy.

Drug toxicity occurs when drug levels exceed the therapeutic range; toxicity may occur secondary to overdose (intentional or unintentional) or drug accumulation. Factors that influence drug toxicity include disease, genetics, and age.

Tolerance and Tachyphylaxis

Tolerance refers to a decreased responsiveness to a drug over the course of therapy; an individual with drug tolerance requires a higher dosage of drug to achieve the same therapeutic response. In contrast, **tachyphylaxis** refers to an acute, rapid decrease in response to a drug; it may occur after the first dose or after several doses. Tachyphylaxis has been demonstrated with drugs such as centrally acting analgesics, nitroglycerin, and ranitidine, to name a few. To provide safe and effective care, nurses must be aware of these potential reasons a patient may fail to respond therapeutically to drug administration.

Placebo Effect

Placebo effect is a drug response not attributed to the chemical properties of the drug. The response can be positive or negative and may be influenced by the beliefs, attitudes, and expectations of the patient. Although the placebo effect is psychological in origin, the response can be physiologic, resulting in changes in heart rate, blood pressure, and pain sensation.

DRUG INTERACTIONS

Seventy percent of Americans are taking one or more prescription drugs. Drug therapy is complex because of the great number of drugs available. Drug-drug, drug-nutrient (e.g., food, supplements, alcohol), drug-disease, and drug-laboratory interactions (when a drug interferes with laboratory testing) are an increasing problem. Because of the possibility of numerous interactions, the nurse must be knowledgeable about drug interactions and must closely monitor patient response to drug therapy. Thorough and timely communication among members of the health team is essential. Patients at high risk for interactions include those who have chronic health conditions, take multiple medications, see more than one health care provider, and use multiple pharmacies. Older adults are at especially high risk for drug interactions because 20% of older adults take five or more medications. Multiple drug interaction checker websites are available on the Internet for both health care personnel and consumer use, such as Drugs.com at www.drugs.com/drug_interactions.html or *Web*MD at www.webmd.com/interaction-checker.

A **drug interaction** is defined as an altered or modified action or effect of a drug as a result of interaction with one or multiple drugs. It should not be confused with drug incompatibility or an adverse drug reaction, an undesirable drug effect that ranges from mild untoward effects to severe toxic effects that include hypersensitivity reaction and anaphylaxis. Drug incompatibility is a chemical or physical reaction that occurs among two or more drugs in vitro. In other words, the reaction occurs between two or more drugs within a syringe, IV bag, or other artificial environment outside of the body.

Drug interactions can be divided into two categories, pharmacokinetic and pharmacodynamic interactions.

Pharmacokinetic Interactions

Pharmacokinetic interactions are changes that occur in the absorption, distribution, metabolism, and excretion of one or more drugs.

Absorption

When a person takes two drugs at the same time, the rate of absorption of one or both drugs can change. A drug can block, decrease, or increase the absorption of another drug. It can do this in one of three ways: (1) by increasing or decreasing gastric emptying time, (2) by changing the gastric pH, or (3) by forming drug complexes.

Drugs that increase the speed of gastric emptying, such as laxatives, may cause an increase in gastric and intestinal motility and a decrease