Woo | Wright

Pharmacotherapeutics for Advanced Practice Nurse Prescribers

SIXTH EDITION

DAVIS edge.
Access your
Online Quizzing

F.A. DAVIS

PREFACE

The increasing volume of pharmacology-related information presents a challenge to acquire and maintain current knowledge of pharmacotherapeutics. This includes the number of new drugs coming on the market each year, the changes in the "best" drugs to use for any given disease state based on the latest research, the influence on patient and practitioner alike of advertising and promotion, new evidence-based guidelines, and restricted formularies. This information creates competing pressures on the prescriber. This book is designed to provide nurse practitioner students and the nurse practitioner in the primary care setting with a thorough, current, and usable pharmacology text and reference to address these challenges.

The design of this book assumes knowledge of basic pharmacology from one's undergraduate education in nursing. Although a brief review of basic pharmacology is presented in **Chapter 2**, the focus of the book is on advanced pharmacology and the role of the advanced practice nurse in pharmacotherapeutics. The authors of the text are practicing nurse practitioners, pharmacists, or selected specialists in a field. The book is written by advanced practice registered nurses, for advanced practice registered nurses.

ORGANIZATION

This text is organized around four distinct content areas: The Foundation, Pharmacotherapeutics With Single Drugs, Pharmacotherapeutics With Multiple Drugs, and Special Drug Treatment Considerations.

Unit I: The Foundation

The 10 chapters in Unit I provide the foundation of advanced pharmacology and the link between this knowledge and professional practice. **Chapter 1**

discusses the role of the advanced practice registered nurse (APRN) in both the United States and Canada as prescriber and the knowledge needed to actualize this role. Current issues about the evolving role and education of these providers are also presented in this edition, including discussion of the Doctor of Nursing Practice.

Discussion of the roles of other advanced practice nurses in prescribing is included. Factors involved in clinical judgment related to prescribing and increasing adherence to the treatment plan are a central focus, and collaboration with other health-care providers is also presented.

The pharmacology knowledge required for rational drug selection requires more depth than that given in undergraduate pharmacology, where the focus is on safe administration of drugs prescribed by someone else. Advanced pharmacology information on receptor reserve and regulation, bioavailability and bioequivalence, metabolism of drugs (including a focus on the cytochrome P450 microsomal enzyme system), half-life, and steady state are provided in **Chapters 2** and **6.** Information central to the prescribing role includes an in-depth discussion of volume of distribution and therapeutic drug monitoring. Volume of distribution is important in prescribing drugs with very large or very small volumes of distribution and for selecting drugs for patients with cardiac or renal failure, during pregnancy, or when a patient is underweight or obese. Knowing what tests to order and when to order them to assess plasma drug levels by bioassay and to monitor for adverse drug reactions are necessary in making choices about when or if dosage alterations are required or drugs need to be stopped. These topics are also covered in **Unit I**. **Chapter 6** also provides a discussion of the role of pharmacogenetics in prescribing.

Legal and professional aspects of the prescriber role are presented in **Chapter 4.** Issues surrounding the legal authority of the APRN to prescribe a drug, the conditions under which the prescription may be written, and how to write the prescription are presented. Risk management issues are also discussed, including informed consent, dealing with multiple providers, and substance abuse and drug-seeking behaviors.

Consideration of drug and food interactions has long been a part of nursing knowledge, but the interrelationship between nutrition and drug therapy beyond these interactions has been largely overlooked. **Chapter 7** provides a discussion of this interrelationship, including nutritional

supplementation and nutrition as therapy. **Chapter 8** discusses the use of herbal therapies.

Chapter 9 has been expanded and now solely focuses on the use of cannabis for medical conditions, as well as legalized medical and recreational use of cannabis.

Cost issues cannot be ignored when making prescribing decisions. **Chapter 10** provides a thorough discussion of the principles and impact of pharmacoeconomics.

Unit II: Pharmacotherapeutics With Single Drugs

Units II and III are organized around specific drugs and the diseases they are used to treat. The chapters in Unit II are organized to provide easy access to information based on specific drug classes. Many practitioners have a personal formulary of drugs they use for disease processes that they commonly see. When presented with a patient requiring drug therapy, they know the class of drug from which they will make a rational drug choice. The information they seek is about drugs within that class that would be most appropriate for their patient. In the 6th edition, large content chapters (endocrine drugs, drugs used to treat infectious diseases, and drugs that affect the immune system) have been broken down into smaller chapters to ease access of information by the reader.

Pharmacokinetics, pharmacodynamics, and pharmacotherapeutics for each drug class are discussed in the chapters in Unit II. These chapters include tables with easy-to-access information on the pharmacokinetic properties of each drug, drug interactions, clinical use and dosing, and available dosing forms. A major focus is on rational drug selection and on monitoring parameters. Patient education specific to each drug class is provided—designed around administration of the drug, adverse drug reactions to monitor for and what to do if they occur, and lifestyle modifications that complement the drug therapy.

To provide the most up-to-date, accurate, and relevant information possible, contributors to this unit are practicing clinicians and the newest published guidelines are consistently used. The “Prescribing Pearls” features, drawn from the daily practice of these contributors, are incorporated throughout the text. Drugs currently in development that may influence drug choices in the near future are also included in the “On the Horizon” features.

Unit III: Pharmacotherapeutics With Multiple Drugs

The chapters in Unit III provide drug information from the viewpoint of the disease processes they are commonly used to treat. Patients often have complex health and illness issues and treatment needs, requiring multiple drugs in different drug classes. Unit III facilitates acquisition of complex prescribing knowledge by providing information from a disease process format. The diseases in this unit are those commonly seen in primary care and for which multidrug therapy from more than one drug class may be recommended. The 6th edition of the text has new chapters on the pharmacological management of COVID-19 **(Chapter 34)** and obesity **(Chapter 45)**. The chapter previously named Alcohol and Drug Abuse has been renamed Substance Use Disorders **(Chapter 49)**.

Pharmacotherapeutics is discussed in Unit III in relation to the pathophysiology of the disease and the goals of treatment. Each chapter explores how patient variables, economic considerations, concurrent diseases, and drug characteristics influence rational drug selection. Evaluating outcomes along with guidelines for consultation and referral are included. Where relevant, the newest published professional guidelines are incorporated. Each patient is unique, and no set of guidelines or treatment algorithm applies to each patient. However, these tools, drawn from the clinical knowledge and experience of experts in a given specialty, are helpful in rational drug selection, especially for the student and novice practitioner. Clinically based case studies, provided in an online supplement to this edition, provide a framework for application of pharmacotherapeutic knowledge.

Unit IV: Special Drug Treatment Considerations

Unit IV focuses on special populations. Age-related variables are explored in **Chapter 55,** "Pediatric Patients," and **Chapter 57,** "Geriatric Patients." Gender variables are considered in **Chapter 53,** "Women as Patients," **Chapter 54,** "Men as Patients," and **Chapter 56,** "Transgender Persons as Patients."

FACULTY AND STUDENT RESOURCES

With each edition of this text, we have added and updated a wide array of resources to enhance student learning and provide faculty support.

Davis Edge Faculty and Student Quiz Bank

Davis Edge is an adaptive platform that affords faculty and students access to over 900 board-style questions, with complete and detailed rationales for all correct answers and incorrect distractors. Davis Edge provides faculty with a powerful assessment tool that seamlessly integrates with learning management systems and gradebooks. As students take quizzes in Davis Edge, the system provides data back to faculty as well, tracking student progress and reporting on areas of student strength and weakness (as individuals and at the cohort level) to assist with remediation. **All questions in Davis Edge are completely different from those in the faculty test bank,** so that quizzing and exams are created from unique and separate question pools.

For students, the Davis Edge platform offers nearly endless opportunities to ensure that they comprehend and retain the information presented in chapters. The program also provides integrated access to the e-book version of the text, so students can quickly look up and refresh their knowledge base as a part of their quizzing experience. Student response to Davis Edge has been overwhelmingly positive, with students affirming that Davis Edge quizzes enhanced their critical thinking skills and made learning and studying more engaging. Faculty report that the Davis Edge quizzes helped their students retain content better and improved the outcomes in their pharmacology courses.

In addition to Davis Edge, online resources for this edition include the following:

- Case Studies. A total of 94 case studies: 47 cases with questions, specifically for students to practice the application of knowledge (instructors provided with answers), and another 47 case studies specifically for instructors to use for classroom activities and discussion (answers accessible only by faculty).
- PowerPoints to support lectures and course packs.
- An updated test bank of nearly 1,000 questions for exam creation.

FEATURES

Throughout the text, care has been taken to provide the reader with a consistent and logical presentation of material. Visual appeal is provided

through the generous use of tables, illustrations, and flowcharts. Other features are unique to the specific units.

Unit I Chapters

In-depth pharmacology base for advanced pharmacotherapeutics
Herbal and complementary therapies
Cannabis
Pharmacogenomics
Nutrition and nutraceuticals as therapy
Pharmacoeconomics

Unit II Chapters

Tables for ease of access to information
  Pharmacokinetics tables
  Drug Interactions tables
  Dosage Schedule tables
Rational drug selection and monitoring parameters
Patient Education
Prescribing Pearls
On the Horizon feature

Unit III Chapters

Integration of pathophysiology and pharmacotherapeutics
Integration of professional treatment guidelines
Drugs Commonly Used tables
Patient Education displays

Unit IV Chapters

Variables related to special populations:

Pediatrics
Geriatrics
Women
Men
Transgender Persons

SUMMARY

Every effort has been made to make this text as comprehensive, accurate, and user-friendly as possible. The generous use of tables for ease of access to information, the focus on rational drug selection, the inclusion of often hard-to-find monitoring parameters, and the integration of patient education throughout the text are examples of this user-friendly approach. The authors hope that you will find this a valuable resource both as a student and in your practice.

TMW
WLW

ACKNOWLEDGMENTS

I would like to acknowledge my mentors who have supported me throughout my nursing career. Included in this list are Dr. Sheila Kodadek, who has been my mentor and friend throughout my nursing career, and the late Dr. Terry Misener, an amazing nurse practitioner and leader.

TMW

I would also like to acknowledge my mentors who have also supported me throughout my NP career. A special shout-out to Dr. Margaret Fitzgerald, who not only educated me during my NP program, but singlehandedly helped to launch my speaking career. To Dr. Pat White, who inspired me to be the NP I was destined to be, and Dr. Mimi Secor, you believed in me from day one. To the late Dr. Susan Neary, your love of teaching inspired me.

WLW

ABOUT THE AUTHORS

TERI MOSER WOO, RN, PhD, ARNP, CPNP-PC, CNL, FAANP

Teri has been a pediatric health-care provider for 40 years. She received her BSN from Oregon Health Sciences University (OHSU) in 1984. Teri earned an MSN in Childrearing Family Nursing in 1989 and a post–Masters Pediatric Nurse Practitioner Certificate in 1993 from OHSU. In 2008, she earned a PhD in Nursing from the University of Colorado College of Nursing, Denver. Teri was president of the Oregon Pediatric Nurse Practitioner Association from 1998 to 2000 and from 2011 to 2013, served on the National Association of Pediatric Nurse Practitioners (NAPNAP) board as a Member at Large 2018 to 2022, and is a Fellow in the American Association of Nurse Practitioners. Dr. Woo was named Oregon Pediatric Nurse Practitioner of the Year in 2001 by the Oregon Pediatric Nurse Practitioner Association, National Primary Care Advocate in 2009 by the Pediatric Nurse Certification Board, and Distinguished Alumna of the Year award by Oregon Health Sciences University School of Nursing in 2014. In 2022 Dr. Woo received the Loretta C. Ford Distinguished Fellow award from NAPNAP. Dr. Woo writes and lectures extensively on the topics of safe prescribing for children and nurse practitioner prescribing. She is a Professor and Director of Nursing at Saint Martin's University in Lacey, Washington. Teri continues to practice as a Pediatric Nurse Practitioner for Mary Bridge Children's Hospital in pediatric urgent care.

WENDY L. WRIGHT, DNP, ANP-BC, FNP-BC, FAANP, FAAN, FNAP

Wendy received her Doctor of Nursing Practice in 2019 from the University of Alabama, Tuscaloosa. She is a 1992 graduate of the Adult Primary Care

Nurse Practitioner program at Simmons College in Boston, Massachusetts, and completed a family nurse practitioner post–master's program in 1995. She is an adult and family nurse practitioner and the owner of a nurse practitioner–owned and –operated clinic in New Hampshire. Her family practice has won numerous awards, including Top Providers in New Hampshire 2020, Top 20 Fastest Growing Family Business, and Top 20 Women-Owned Business in New Hampshire. In addition, she is the Owner of Partners in Healthcare Education, a medical education company. She is the past president of NPACE and the senior lecturer for Fitzgerald Health Education Associates.

She is the recipient of numerous awards and was chosen by the American Association of Nurse Practitioners as the 1999 recipient of the New Hampshire State Excellence Award. In addition, she received the 2009 New Hampshire Nurse Practitioner of the Year, the 2014 Top 5 Women in New Hampshire Business Award, and in 2018, one of the top 10 NPs in America. In 2020 and 2022, Dr. Wright won the Top Doctor in Souhegan Valley and the 2021 State of New Hampshire Advocate of the Year Award. In 2005, she was inducted as a Fellow into the American Academy of Nurse Practitioners; in October 2014, a Fellow into the American Academy of Nursing; and in March 2017, a Fellow into the National Academies of Practice.

She is the founder of the New Hampshire Chamber of Entrepreneurial Nurse Practitioners, an organization designed to assist nurse practitioners with independent practice issues. In addition to full-time clinical practice, she presents nationally to different audiences and has been a speaker at over 1,000 conferences in 47 states. She has been a medical media spokesperson for numerous companies and has appeared on radio, on television, and in print magazines. In October 2020, Dr. Wright was featured in the *Wall Street Journal* for her nurse practitioner–led clinics and the care they provide. Wendy is frequently consulted by malpractice attorneys around the area of clinical practice and has worked on more than 100 malpractice cases involving nurses and nurse practitioners.

Dr. Wright has more than 50 publications in peer-reviewed journals; a textbook, *Adult Health History and Physical Examination Cue Cards;* and a personal memoir written with her elementary school friend, *Breaking the Cycle,* by Beckwith and Wright.

CONTRIBUTORS

Anthony M. Angelow, PhD, ACNPC, ACNP-BC, AGACNP-BC, CEN, FAEN, FAANP

Associate Clinical Professor and Chair, Advanced Practice Nursing
College of Nursing and Health Professions
Drexel University
Philadelphia, Pennsylvania

Cally Elizabeth Bartley, MS, FNP

Senior Instructor
Family Nurse Practitioner
University of Colorado School of Medicine
Aurora, Colorado

Mary Ellen Biggerstaff, DNP, FNP, MPH

Assistant Professor
Frontier Nursing University
Versailles, Kentucky
Family Nurse Practitioner
Summit Pacific Wellness Center
Elma, Washington

John Michael Bowen, MSN, ACNP-BC

Nurse Practitioner
University of Alabama
Birmingham, Alabama

Aimee Susanne Bucci, DNP, CPNP-AC

Instructor
Edson College of Nursing and Health Innovation
Arizona State University
Phoenix, Arizona

Catherine Michelle Carman, MSN, FNP-C

Nurse Practitioner
Georgia Urology
Austell, Georgia

Jason Chau, PharmD

Pharmacy Clinical Programs Coordinator
Kaiser Permanente
Renton, Washington

Lisa A. Cranwell-Bruce, DNP, FNP-C

Clinical Associate Professor
Georgia State University
Atlanta, Georgia

Michelle Renee Dickens, MSN, RN, FNP-C, AE-C

Nurse Practitioner/Certified Asthma Educator
Ferrell Duncan Clinic Allergy & Immunology
Springfield, Missouri

Gina Dobbs, DNP, CRNP

Nurse Practitioner and Sub-Investigator
1917 HIV/AIDS Outpatient/Research Clinic
University of Alabama at Birmingham
Birmingham, Alabama

Kim Ferguson DNP, FNP-BC

Assistant Professor
College of Nursing
East Tennessee State University
Johnson City, Tennessee

Jennifer Fisher, DNP, WHNP-BC

Assistant Professor and Co-Specialty Director of the WHNP Program
College of Nursing
University of Colorado Anschutz Medical Campus
Aurora, Colorado

Angela Golden, DNP, FNP-C, FAANP

Owner, Clinician
NP Obesity Treatment Clinic
Flagstaff, Arizona

Ryan Seth Holley-Mallo, PhD, DNP, NP-C, FAANP

Associate Professor of Graduate Nursing
Averett University
Danville, Virginia

Randall S. Hudspeth, PhD, MBA, MS, APRN-CNP, FRE, FAANP

Executive, Clinical Practice Consultant
R.S. Hudspeth Consulting, LLC
Boise, Idaho

Amanda Johnson, DNP, CPNP-PC/AC

Neurosurgery Nurse Practitioner/Assistant Professor
University of Chicago/Rush University
Chicago, Illinois

Tracy Klein, PhD, FNP, ARNP, FAANP, FAAN

Associate Professor
College of Nursing
Assistant Director, Center for Cannabis Policy, Research and Outreach
Washington State University, Vancouver
Vancouver, Washington

Patrice Janee Laster, DNP, ARNP, FNP-BC

Advance Practice Provider
Seattle Children's Hospital Odessa Brown Clinic
Seattle, Washington

Maureen A. Madden, DNP, CPNP-AC, CCRN, FCCM, FAAN

Professor/Nurse Practitioner Pediatric Critical Care
Rutgers Robert Wood Johnson Medical School
New Brunswick, New Jersey

Theresa Mallick-Searle, MS, PMGT-BC, ANP-BC

Adult Nurse Practitioner, Pain Medicine
Division of Pain Medicine, Stanford Health Care
Redwood City, California

Dawn Marie Mason, MSN, PMHNP-BC, PMHS, CPNP-PC

Psychiatric Mental Health NP/Consulting Associate Faculty
Duke University of Nursing/Duke Health
Durham, North Carolina

Fujio McPherson, DAOM, ARNP, LAc Dipl Ac LTC (ret)

Family Nurse Practitioner
Madigan Army Medical Center
Joint Base Lewis McCord, Washington
and
Cofounder of Acupuncture & Integrative Medicine Institute
Olympia, Washington

Mikki Meadows-Oliver, PhD, APRN, PNP, FAAN, FAANP

Clinical Professor
New York University
New York, New York

Sally K. Miller, PhD, APRN, PMHNP-BC, FNP-BC, AGACNP-BC, AGPCNP-BC

Clinical Professor
Drexel University College of Nursing and Health Professions
Philadelphia, Pennsylvania

Anne E. Morgan, PharmD

Clinical Pharmacy Specialist, Department of Neurology
University of Colorado Hospital
Aurora, Colorado

Hilda Bi Ndikum, PharmD, MPH

Senior Instructor, Department of Clinical Pharmacy
Skaggs School of Pharmacy and Pharmaceutical Sciences
University of Colorado Anschutz Medical Campus
Aurora, Colorado

Elizabeth Marie Nutter, DNP, ARNP, CNM, FACNM

Assistant Professor
Saint Martin's University
Lacey, Washington

Vanessa Pomarico-Denino, EdD, FNP-BC, FAANP

Lead Clinician, Diversity, Equity and Inclusion, Northeast Medical Group
Quinnipiac University
Hamden, Connecticut

James Raper, PhD, CRNP, JD, FAANP, FAAN, FIDSA

Director and Professor of Medicine and Nursing
University of Alabama at Birmingham
Birmingham, Alabama

Peter J. Rice, PharmD, PhD, BCPS, FAPhA

Professor, Department of Clinical Pharmacy
University of Colorado Anschutz Medical Campus
Aurora, Colorado

Joyce L. Ross, MSN, CRNP, CLS, FNLA, FPCNA

CRNP Educator
University of Pennsylvania
Philadelphia, Pennsylvania

Danielle Kathlyn Sebbens, DNP, CPNP-AC/PC

Associate Director, Doctor of Nursing Practice Program, Clinical Associate Professor
Edson College of Nursing and Health Innovation, Arizona State University
Phoenix, Arizona

Leah Foster Smith, MSN, APRN, FNP-BC, CNN-NP, FNKF

Director of Advanced Practice Providers
Metrolina Nephrology Associates
Charlotte, North Carolina

Sheila K. Smith, PhD, RN, ANP-BC, AGACNP-BC, ARNP, CNP, FAANP

Clinical Professor and AGPCNP Program Coordinator
School of Nursing
University of Minnesota
Minneapolis, Minnesota

Regena Spratling, PhD, RN, APRN, CPNP-PC, FAANP, FAAN

Professor of Nursing
Georgia State University
Atlanta, Georgia

R. Brigg Turner, PharmD

Clinical Manager
OHSU–Hillsboro Medical Center
Hillsboro, Oregon

Connie A. Valdez, PharmD

Professor
University of Colorado Anschutz Medical Campus
Aurora, Colorado

Susan S. VanBeuge, DNP, APRN, FNP-BC, FAANP, FAAN

Professor in Residence
University of Nevada, Las Vegas
Las Vegas, Nevada

Sarah Kay Wickenhagen, DNP, FNP-C, APRN

Clinical Assistant Professor, Nurse Practitioner, Policy Analyst
Oregon Health & Science University, Salem Hospital, Oregon Board of Nursing
Canby, Oregon

Kenneth Wysocki, PhD, FNP, FAANP

Nurse Practitioner
Optum/United Healthcare
Phoenix, Arizona

Tracy Diane Yep, PharmD, MS, BCACP

Pharmacy Clinical Programs Coordinator
Kaiser Permanente Washington
Renton, Washington

REVIEWERS

Michele S. Bednarzyk, DNP, FNP-BC

Associate Clinical Professor/Program Director FNP/DNP
University of North Florida
Jacksonville, Florida

Dana Clawson, DNS, WHNP-BC, CNE

Professor of Nursing Doctoral Studies
Northwestern State University
Shreveport, Louisiana

Evelyn Duffy, DNP, AGPCNP-BC, FAANP

Florence Cellar Professor of Gerontological Nursing
Frances Payne Bolton School of Nursing CWRU
Cleveland, Ohio

Cheryl Jackson, DNP, CRNP

Assistant Professor
Bloomsburg University
Bloomsburg, Pennsylvania

Julie Ann Koch, DNP, APRN, FNP-BC, FAANP

Associate Professor, Emeritus
Valparaiso University
Valparaiso, Indiana

Angela Patricia Lukomski, DNP, RN, CPNP-PC

Professor/Pediatric Nurse Practitioner
Eastern Michigan University
Ypsilanti, Michigan

Elizabeth Phenneger, DNP, ARNP, FNP-C

Clinical Assistant Professor
Washington State University
Spokane, Washington

Brandy Smith, DNP, APRN, FNP-BC

Assistant Professor of Nursing
Delta State University
Cleveland, Mississippi

Douglas J. Stephens, DNP, CRNP, ACNP-BC

Assistant Professor
Jacksonville State University
Jacksonville, Alabama

Marjorie A. Vogt, PhD, DNP, APRN

Associate Director, School of Nursing, DNP Program Director
Ohio University
Athens, Ohio

Jill E. Winland-Brown, EdD, FNP-BC, FAANP

Professor Emeritus
Florida Atlantic University
Port St. Lucie, Florida

CONTENTS

UNIT I. THE FOUNDATION

UNIT I

THE FOUNDATION

CHAPTER 1

THE ROLE OF THE ADVANCED PRACTICE NURSE AS PRESCRIBER

Teri Moser Woo • Wendy L. Wright

Nurses administer medications prescribed by another provider as part of their role in caring for patients. The knowledge base to safely administer medications is an integral part of basic nursing education. Advanced practice nurses require additional knowledge to safely prescribe medications beyond what is taught in prelicensure nursing programs. Additionally, the prescriber role requires the willingness and ability to assume a different level of responsibility to the patient. Advanced practice nurses other than nurse practitioners (NPs) may gain prescriptive authority or prescribe under protocol; therefore, the term *advanced practice registered nurse* (APRN) is used in this chapter to include NPs, certified nurse midwives (CNMs), certified registered nurse anesthetists (CRNAs), and clinical nurse specialists (CNSs) with prescribing authority, as determined by the individual state's nurse practice act.

ROLES OF REGISTERED NURSES IN MEDICATION MANAGEMENT

Registered Nurses

Experienced registered nurses (RNs) often find themselves in the position of discussing what might be the "best" drug a patient should receive with an APRN or a physician. RNs are advocates for the patient, and their input should be sought and highly valued in the prescribing process. Collaboration between the nurse and prescriber improves patient safety and the quality of care the patient receives; however, the responsibility for the final decision regarding which medication to prescribe remains with the prescriber.

Advanced Practice Registered Nurses

APRNs have a higher level of responsibility related to pharmacotherapeutics than RNs. The nature of this responsibility depends on whether the APRN can prescribe medications. States vary in their laws related to prescriptive authority for APRNs. Twenty-eight states and Guam have fully independent prescribing by nurse practitioners (American Association of Nurse Practitioners [AANP], 2023). Some states have full or limited prescribing allowed by CNSs, including Alaska, Colorado, Connecticut, Hawaii, Iowa, Idaho, Minnesota, Montana, Nevada, New Mexico, North Dakota, Oregon, Utah, Vermont, the District of Columbia, West Virginia, and Wyoming (National Council of State Boards of Nursing, 2018).

Because nonprescribing APRNs have in-depth knowledge of the drugs used in their specialty areas, their collaboration with the health-care providers who are prescribing is valuable. They may assist in determining the pharmacotherapeutic protocols for their patients and may be credentialed by their organization to select drugs within those protocols to be administered to their patients. These roles related to pharmacotherapeutics represent an intermediate level of responsibility between the staff RN, who administers drugs chosen by another provider, and the NP, who prescribes a drug without the need for a protocol. APRNs also collaborate with other providers in designing and implementing research protocols to test the efficacy of a new drug. In addition, they have a central role in educating nurses and other providers in the appropriate use of those new drugs.

ROLES AND RESPONSIBILITIES OF APRN PRESCRIBERS

APRNs exist in a range of practices and include CRNAs, CNMs, and others whose titles include the words *nurse practitioner* or *advanced practice registered nurse.* The responsibility for the final decision on which drug to use and how to use it is in the hands of the APRN prescriber. The degree of autonomy in this role and the breadth of drugs that can be prescribed vary from state to state based on the nurse practice act of that state.

The 2010 Institute of Medicine (IOM) publication *Future of Nursing: Leading Change, Advancing Health* called for removing scope of practice barriers and allowing NPs to practice to the full extent of their education

and training (IOM, 2010). Significant progress has been made since the 2010 report, but barriers to full practice authority remain, which affect patients' ability to receive care (National Academies of Science, Engineering, and Medicine, 2021).

Each year, there are multiple advances in NP practice across the United States, and the January issue of the *Nurse Practitioner* journal and an issue of the *American Journal for Nurse Practitioners* present a legislative update providing a summary of each state's practice acts as they relate to titling, roles, and prescriptive authority. As of March 2023 (AANP, 2023), the following were true of NP regulation of practice and prescribing authority:

- All states have title protection for NPs.
- Only Oregon has mandated third-party reimbursement parity for NP services.
- Mississippi has enacted Medicaid reimbursement at 100% for NPs and 90% for CRNAs and CNMs.
- In all but five states, the control of practice and licensure is within the sole authority of the state's board of nursing. These five states have joint control in the board of nursing and the board of medicine.
- Scope of practice is determined by the individual NP's license under the nurse practice act of the licensing jurisdiction. Some have a graduated scope based on experience level. New prescribers need to understand that their employment sites may restrict this legal scope of practice but cannot extend it.
- In 27 states, the District of Columbia, and Guam, NPs have independent scope of practice and prescriptive authority without a requirement or attestation for physician collaboration, consultation, delegation, or supervision.
- Twelve states have full autonomous practice and prescriptive authority following a period of postlicensure/postcertification supervision or collaboration.
- Two states, Georgia and Oklahoma, do not allow NPs to prescribe Schedule II medications. Louisiana restricts Schedule II prescribing by NPs for obesity and chronic pain. Arkansas and Missouri restrict NP prescribing of Schedule II drugs to hydrocodone combination products,

and South Carolina NPs must have Schedule II prescribing outlined in their practice agreement (AANP, 2023).

ADVANCED KNOWLEDGE

General knowledge about the pharmacokinetics and pharmacodynamics of drugs, how to administer them safely, and what to teach the patient is learned in undergraduate nursing courses and subsequently refined in practice. Additional knowledge, critical thinking, and assumption of a higher level of legal responsibility are required to assume the prescriber role. Knowledge of medicine, pharmacology, and nursing intertwine in the NP role. As a prescriber, it becomes the role and responsibility of the NP to determine the diagnosis for which the drug will be prescribed, prescribe the appropriate drug, monitor the expected outcome of the drug, and incorporate a holistic assessment of the impact of disease and therapy on patient lives.

The APRN role requires advanced knowledge about pathophysiology, medical diagnoses, and pharmacology to choose an appropriate drug. Determining the medical diagnosis is not within the scope of this book, but rational drug selection requires knowledge of the disease processes (medical diagnoses) for which a drug may be prescribed and the mechanism of action of a specific drug and how it affects this disease process. Rational drug selection is discussed throughout the book.

The prescriber role requires advanced pharmacology knowledge beyond that taught in basic nursing education. Knowledge required for rational drug selection includes, for example, bioequivalence and cost when deciding whether to use a generic form of a given drug; the enzyme systems used to metabolize a drug for deciding about potential drug interactions; and the pharmacokinetics of a drug for determining the loading, maintenance, and tapering doses. The terms may sound familiar, but the underlying depth of information and the role of this information in determining the best drug to prescribe are beyond basic nursing pharmacology knowledge. Volume of distribution, for example, receives little discussion in undergraduate nursing pharmacology texts, but it is often critical in determining dosage for drugs with very large or small volumes of distribution and in selecting drugs for patients with cardiac or renal failure, pregnant patients, or patients who are underweight or obese. Assessment of plasma drug levels by bioassay may

be a familiar concept, but using this knowledge to determine whether a drug should be prescribed or a prescription altered will be new. The RN may know a given drug's effect on renal functioning, but the prescribing APRN needs to know what tests to order and when to appropriately monitor that functioning, as well as when or if to alter the dosage or stop the drug. Diagnostic tests and their role in drug monitoring may be briefly covered in a basic nursing pharmacology course, but appropriate modification of drug therapy based on results is added knowledge that an APRN needs to prescribe safely.

A nurse who is studying to be an APRN will need additional knowledge about prescriptive authority. Does the chosen drug fit within the legal authority of an APRN to prescribe in their state? What are the conditions under which the prescription may be written, and how does one correctly write it? What constraints may be in place because of the patient's health insurer or lack of health insurance?

Additionally, the APRN needs to be aware of new drugs introduced to the market, medication alerts, and label changes due to postmarketing analysis. In 2022, there were 37 novel drug entities approved by the U.S. Food and Drug Administration (FDA), with up to 59 new drugs approved annually (U.S. FDA, Center for Drug Evaluation and Research, 2023). The FDA sends out alerts to health-care providers via the MedWatch Safety Alert system as new information becomes available from postmarketing surveillance and modifies drug labels as appropriate. Prescribers can file a MedWatch safety report if they are concerned about an unexplained reaction to any prescription or over-the-counter medication or supplement. Ever-changing drug information requires the APRN to remain up to date at all times.

BENEFITS OF AN APRN AS PRESCRIBER

Although the focus of this book is on pharmacotherapeutic intervention, alternative treatment options are also part of the armamentarium that can be used to treat a given disorder and may interact with the pharmacotherapeutic intervention. Discussion of common therapies that may be chosen as treatment options or that are integral to drug therapy is integrated throughout the drug-specific and disease-specific chapters.

Some therapies have traditionally been part of what all nurses teach, and they remain central to the role of the APRN—for example, lifestyle management issues for a cardiac patient, relaxation techniques for a patient experiencing stress, and appropriate exercise for a patient with low back pain or arthritis. Herbal therapies have been part of the health practices of people throughout history, but it is only recently that health-care providers have acknowledged them and considered them in planning treatment. If the APRN chooses to use herbal therapy or the patient is using this therapy either independently or as suggested by another provider, there must be reliable resources about the therapy and its impact on prescribing. This book includes a separate chapter on herbal therapy and the uses of complementary therapies and also integrates the use of herbal interventions throughout.

Nutrition is also a common issue in nursing, but often the nurse's knowledge of nutrition related to pharmacology is limited to food–drug interactions or the low-sodium diet for a patient with hypertension. Knowledge regarding the effect of foods and nutrition on drug prescribing is integrated throughout the book, and foods used as therapy are included in Chapter 7.

Choosing among pharmacological and other treatment options also involves advanced knowledge. The right choice depends on accurate information about the patient and his or her situation and the effects of any alternative treatment options on health outcomes. Choices also depend on the patient's culture, preferences for different health outcomes, attitudes toward taking risks, and willingness to endure often uncomfortable adverse drug effects during treatment for some possible future benefit.

Characteristics of APRNs and their practice are consideration of the whole patient, the joint setting of therapeutic goals with other members of the health-care team, and the inclusion of the patient in each decision about care. This holistic approach remains a central element in APRN practice and is often cited by patients and other providers as a hallmark and distinguishing feature of APRN practice compared with other primary care providers.

CLINICAL JUDGMENT IN PRESCRIBING

Prescribing a drug results from clinical judgment based on a thorough assessment of the patient and the patient's environment, the determination of medical and nursing diagnoses, a review of potential alternative therapies, and specific knowledge about the drug chosen and the disease process it is designed to treat. In general, the best therapy is the least invasive, least expensive, and least likely to cause adverse reactions. Frequently, the best choice is to have lifestyle, nonpharmacological, and pharmacological therapies working together. When the choice of treatment options is a drug, the advanced practice nurse prescribing the drug needs to consider the questions outlined in Box 1–1. Chapter 3 discusses rational drug selection in depth.

Nurses evaluate sources of drug information and learn which ones to trust. For an APRN, the sources of drug information expand to include published guidelines; professional literature, from well-reputed journals to literature from specialty and professional organizations; a multitude of computerized drug databases (e.g., Micromedix, Lexicomp); information from the FDA; and formula programs that can be accessed via smartphone or computer.

The APRN prescriber needs to evaluate how reliable the drug information is. How can reliability be determined? Is the resource written by someone who may benefit from presenting biased information? Is the information source current? Today's "wonder drug" may be removed from the market tomorrow. Is the information relevant to the specific patient for whom the drug will be prescribed? If the information is a research report, what type of research design was used? Are there questions about the validity and reliability of the data? Are national or international guidelines used to inform prescribing, or does the reference suggest prescribing outside established guidelines? To prescribe drugs appropriately, APRNs must be able to answer these questions. To do this, they must master sources of reliable information and use them on a regular basis.

COLLABORATION WITH OTHER PROVIDERS

No single member of the health-care team can provide high-quality care without collaborating with other team members. Teams most often comprise physicians, pharmacists, podiatrists, mental health specialists, therapists,

and other providers, including APRNs who are not NPs, physician assistants (PAs), and other nurses.

BOX 1– QUESTIONS TO ASK WHEN PRESCRIBING 1

- Is there a clear indication for drug therapy?
- What drugs are effective in treating this disorder?
- What is the goal of therapy with this drug?
- Under what conditions is it determined that a drug is not meeting the goal and a different therapy or drug should be tried?
- Are there unnecessary duplications with other drugs that the patient is already taking?
- Would an over-the-counter drug be just as useful as a prescription drug?
- What is the cost of the medication, and what is the coverage?
- Where is the information to answer these questions?

Physicians

Collaboration with physicians has been something of a roller-coaster ride for NPs. Early in the development of the NP role, physicians were the teachers in NP programs and accepted NPs as physician-extenders. As the role of the NP evolved to clearly indicate that it was advanced nursing practice, and as legislation made autonomy of practice possible, the relationship became more adversarial, with the American Medical Association (AMA) issuing statements regarding the NP and PA scope of practice (AMA, 2023), often for economic reasons. The AMA opposed the Department of Veterans Affairs (VA) decision to allow full practice authority for APRNs and continues to register opposition to CRNAs gaining full practice authority after the initial ruling.

Although this struggle continues at the national level, NPs and physicians do work together very effectively on an individual basis and in collegial care teams. In an era of health-care reform, team members' joint concerns about patient care decisions require them to be allies.

A physician's expertise related to pharmacology is based on understanding biochemistry and prescribing for a given pathophysiology. APRNs traditionally approach prescribing drugs slightly differently from physicians. As APRNs prescribe a drug for a given pathophysiology, their nursing background leads them to place equal emphasis on understanding

the impact the drug will have on the patient. Patient education is a central focus of nursing and APRN practice. Knowledge and clinical experience shared from the mingling of medical and nursing perspectives are mutually beneficial to the providers and the patient. The APRN can benefit from the in-depth knowledge about the drugs in the physician's specialty area. The physician can benefit from the APRN's focus on the impact of the drug on the patient and from their patient education skills. In the age of health-care reform, increasing emphasis is being placed on these latter issues.

Pharmacists

Collaboration with pharmacists requires an understanding of the educational preparation for and evolution of the role of the pharmacist. The profession of pharmacy requires graduate-level preparation for all pharmacists with the granting of a practice doctorate, the Doctor of Pharmacy (PharmD). PharmDs have extensive knowledge about pathophysiology and take an active role in determining the best drug to prescribe. A PharmD can assist by offering expertise on the clinical management of patients, including available dosage forms, potential adverse reactions, and drug interactions. Both physicians and APRNs increasingly consult PharmDs for their knowledge of pharmacokinetics and pharmacotherapeutics when prescribing for complex patients. In some jurisdictions, PharmDs have some independent prescriptive authority.

Other APRNs

Collaboration with other NPs and APRNs who have prescriptive privileges has two major advantages. On a one-to-one basis dealing with individual patient issues, NPs and APRNs can share "pearls" from their knowledge base and collaborate to improve the care of the patient. Collaboration on issues related to scope of practice and prescriptive privilege at the state and national level is critical to obtaining and maintaining the autonomy of practice needed to provide optimal patient care.

Physician Assistants

The focus of the PA's practice is similar to that of the physician, so both the APRN and the PA can benefit from interaction with each other in much the same way as from their interaction with physicians. Many PAs desire more autonomy in their practice, and the experience of APRNs in developing

autonomy may be helpful. At this time, such autonomy does not exist, so it is important to know the laws that govern the practice of the PA as well as the APRN in the state to determine how collaboration can best occur.

Nurses Not in Advanced Practice Roles

APRNs regularly collaborate with other nurse colleagues who are not in advanced practice roles. Some have specialized knowledge, such as Certified Diabetes Educators (CDEs) and wound and ostomy care specialists (WOCS). These nurses and their assistants carry out the prescriptive orders of the APRN. For each of these care providers, it is important to remember their preparation, knowledge level, and legal responsibility in carrying out the APRN's orders.

RNs and licensed practical/vocational nurses function under their own licenses. Their preparation and responsibility are defined by the nurse practice act in each state. Whether they can legally take orders from an APRN is also delineated in these statutes. When prescribing drugs that others will administer, APRNs must know the nurse practice act in the state in which they practice. Medical assistants (MAs) may have certification in the state that delineates their preparation, but they are generally not licensed. Their knowledge of drugs may be limited, if they have had any formal education in the area of pharmacology beyond administration. When prescribing drugs to be administered by MAs, APRNs must ensure that MAs clearly understand what they are to do; careful oversight is critical.

CANADIAN NURSE PRACTITIONER PRACTICE

There are more than 7,400 APRNs in Canada (Canadian Institute for Health Information, 2023). As in the United States, where APRN scope of practice and regulation vary from state to state, NP scope of practice and regulation in Canada vary from province to province. NPs practice independently in Canada, but the scope of practice for NPs also varies from province to province, as well as by practice setting. There are now pediatric, family practice, adult, and anesthesia NPs who can prescribe in Canada. Mental health NPs are working on prescriptive authority and currently must qualify as a prescribing NP in either adult, pediatric, or primary care. In 2019, the Canadian Nurses Association published *Advanced Practice Nursing: A Pan-Canadian Framework* to promote a common understanding of the role

of the advanced practice nurse in Canada; this resource defines roles, education, regulation, and evaluation of the nurse practitioner and the clinical nurse specialist in Canada.

In 2012, the Canadian federal government approved the New Classes of Practitioner Regulations (NCPR) under the Controlled Drugs and Substances Act and removed federal restrictions on NP authority to prescribe controlled substances. NCPR allows NPs to prescribe medications included in the Controlled Drugs and Substances Act when treating patients if they are authorized to do so under provincial/territorial legislation. Each individual province and territory must individually implement the NP scope of practice to include prescribing controlled substances.

FACILITATING POSITIVE PRESCRIBING OUTCOMES

Key to successful prescribing is having a patient-centered approach, which results in the desired outcomes of improved health and maximized functional outcomes. Prescribing is not a one-sided responsibility. Patients also have a role in the development of therapeutic plans and then following through on those plans. Unfortunately, the problem of poor adherence to drug therapy is widespread around the world. The FDA estimates that between 30% and 50% of patients adhere to their drug regimen (U.S. FDA, 2016). Nonadherence costs $100 to $300 billion in direct health care costs in the United States annually. The Centers for Disease Control and Prevention (CDC) found that 30% of new prescriptions are never filled (Neiman et al, 2017). Chronic disease patients are more likely to have spotty adherence. Those at highest risk include patients who have asymptomatic conditions, chronic conditions, cognitive impairment, psychiatric illness, or disorders requiring significant lifestyle changes (e.g., smoking cessation), and those who are on complex regimens with multiple daily dosing and significant adverse reactions (Luthy et al, 2008; Sarver & Murphy, 2009; Neiman et al, 2017). When patients' interactions with the provider include poor communication (Fortuna et al, 2018), the risk of nonadherence is even higher.

Nonadherence to pharmacological regimens can lead to failure to reach the desired treatment goal, which may be very costly to the patient and society. Patients who stop using their drugs have more complications from their disease, which results in total increased cost for themselves and the

health-care system. The health-care system itself creates barriers to adherence by limiting access to health care; using restricted formularies; and having prohibitively high drug costs, co-payments, or both. More than $290 billion in unnecessary emergency department and health-care costs related to adherence issues are estimated to occur in the United States every year (U.S. FDA, 2016). Mortality rates double for cardiovascular and diabetic patients who do not follow their treatment plans.

Intentional Versus Nonintentional Nonadherence

Taking or not taking medications may happen for a variety of reasons and may be intentional or inadvertent. Unintentional nonadherence can be attributed to forgetfulness (especially if it is a side effect of a drug), lack of knowledge, dementia, mental health problems, simple procrastination, or an overextended lifestyle.

Not perceiving the usefulness of a medication for symptom resolution or adverse drug reactions are sources of intentional nonadherence. Whether people believe the medication is ineffective, are unaware of the subtlety of its actions, or become frustrated with a "lack of cure" can contribute to whether they take medications as prescribed. Drug costs may also be a factor in intentional nonadherence.

Adverse Drug Reactions

Real or perceived adverse reactions directly affect the outcome of a prescribed drug regimen. If a patient reports a prescribed drug is causing a reaction, then the provider should explore alternative options to treat the problem. Encouraging open communication about these concerns and perceptions is important. Patient perceptions are critical in making the decision to expend finances for a drug (Brody, 2017; Goldsmith et al, 2017).

Certain adverse reactions are more likely to produce nonadherence than others. The ones most likely to produce nonadherence are the "irritating" ones that interfere with the patient's ability to carry out activities of daily living, including what he or she may do for a living. These reactions include headache, dizziness, anorexia, nausea and vomiting, constipation, sexual dysfunction, and diarrhea. Unfortunately, these are also the most common adverse reactions.

Asymptomatic Conditions

A variety of disease states are essentially asymptomatic until their later stages. Most can be treated with drugs in the early stages to prevent their progression; however, it may be difficult to convince a patient of the necessity when there is no overt indication of the disorder except the provider's word. It is even more problematic when the drugs given to treat this "invisible" disorder produce "disease symptoms" themselves.

Chronic Conditions

One out of every two Americans has at least one chronic condition (Neiman et al, 2017). Chronic diseases account for three-fourths of the nation's $1.4 trillion in medical care costs and one-third of the years of potential life lost before age 65. Building support mechanisms and setting up monitoring for patients with chronic disease are critical to their adherence to their regimens. Early phone contacts enable the provider to determine whether the information shared in the clinic has been clearly understood and is being followed. Such follow-up contacts not only help with adherence but also contribute to building a stronger patient–provider relationship (Lyles et al, 2016). Smartphone apps and text messaging may be used to assist with medication adherence (Islam et al, 2022; Simon et al, 2022). Factors contributing to medication adherence are shown in Table 1–1.

Table 1–1 Factors Contributing to Medication Adherence With Chronic Illness

Understanding Treatment Regimen	Beliefs in Effectiveness
Fitting with current routine	Cultural relevancy
Having the skills to carry out the regimen	The staging of disease and level of wellness
Fear of side effects	The ability to control side effects
Remembering to take the medications	Mental health
Family/caregiver support	Interaction with street drugs
Personal views of health	Trust in provider

Adapted from Frank, L., & Miramontes, H. (1998). *Health care provider adherence curriculum.* Pittsburgh, PA: AIDS Education and Training Centers Program.

Knowledge Deficit

Understanding the disease state and the treatment regimen plays a role in adherence. Providing educational material alone, written or oral, cannot ensure that the patient will not have a knowledge deficit regarding the drug regimen or that she or he will be adherent. The quality of the communication and interaction that occur during clinic time is most important. Patients report greater adherence to a drug regimen if they feel that their concerns and specific points of knowledge deficit are addressed during the encounter or during postencounter contacts by the office staff nurse, group visits, and telehealth. The keys to patient education are presented in Table 1–2.

Table 1– 2 Keys for Education to Enhance Adherence

Key Task	Quality Indicator
Simple and critical points	Includes safety information at sixth-grade level
Clear language in native tongue	Supports the Clear Communication initiative (CDC, 2023)
Take time to explain it	Have them "teach back" to ensure understanding
Include family and caregivers	Engages and supports caregivers so that health behaviors are reinforced
Patient participation in plan	Patient-Centered Care Model
Identification of barriers to success	Motivational interviewing
Incorporate staff callbacks and electronic messaging	Use of proven adherence tools
Use certified interpreters for language, hearing, and speech impairments	Provider liable for poor outcomes if lay interpreter is used

Based on CDC, 2023; Robinson, 2016; and Sakraida & Robinson, 2009.

Cognitive Impairment and Psychiatric Illness

Communicating effectively with patients who have cognitive impairment (e.g., Alzheimer disease) can be a challenge. Each person has a different constellation of abilities and needs for support in understanding and remembering. Assessing the abilities of each patient is important to maximizing adherence. This may include help from family, caregivers, friends, and other providers.

Patients with psychiatric illnesses may have difficulty adhering to their drug regimen. Major factors involved with poor adherence include the following: (1) Psychiatric illness has a social stigma, so patients may not seek routine care. (2) The presence of symptoms may result in thoughts and behaviors that do not foster adherence—for example, paranoia, agitation, or

depression. (3) The adverse effects of psychotropics—for example, dizziness, orthostatic hypotension, blurred vision, decreased central processing, and confusion—are effects commonly associated with nonadherence (Cahaya et al, 2022; Yalçin et al, 2019). New transdermal and long-acting oral and injectable psychotropics improve adherence to treatment (Taub et al, 2022).

Longer-Acting Drugs

Selecting drugs with longer half-lives may reduce the likelihood of drug withdrawal symptoms and the return of illness. For example, fluoxetine (Prozac), a selective serotonin reuptake inhibitor used to treat depression, has a 2-week duration of action so that missing doses or stopping the drug altogether produces a long taper and gives the provider time to discover the problem and work to correct it. Drugs for a variety of medical issues are being developed in depot formulations that are long-acting and require only weekly or monthly dosing. These agents combine better efficacy and tolerability with improved adherence.

Use of Reinforcements

The use of reinforcements such as monetary rewards or vouchers, frequent contact with the patient, and personalized reminders can improve adherence (Hoskins et al, 2019). Educational approaches appear to be most effective when combined with behavioral techniques and supportive services, including reinforcements. The use of web-based and smartphone apps works on this principle, where frequent messages create patterns of better adherence and personal involvement in self-care (Chun-Yun Kang, 2022; Simon et al, 2022).

Caregivers

When the patient is a child, an adult with cognitive deficits or disabilities, or a person with mental illness, the patient's caregiver must be involved in the educational process. The caregiver can provide valuable information regarding the patient's responses to drugs or difficulties adhering to the prescribed medication regimen, including adverse reactions. The caregiver may need one-on-one interventions to help adhere to the drug regimen. By exploring the psychological, physical, and social effects of giving care, the provider is acknowledging the difficulties the caregiver must face every day.

Behavioral therapy can empower the caregiver to provide appropriate interventions. Discuss situations in which the patient does not cooperate with their care, including drug therapy. Help the caregiver to remember the times the patient did cooperate, and try to determine what the characteristics of the situation were that elicited that cooperation. Techniques to elicit cooperation can then become part of routine care.

The Pediatric Patient

Achieving full adherence in pediatric patients requires the cooperation not only of the child but also of an adherent parent or caregiver. Adolescent patients may create challenges, given the unique developmental, psychosocial, and lifestyle issues implicit in adolescence. Special interventions for children are discussed in the chapter on pediatric patients (Chapter 55).

Personalized Drug Schedules

Education for the patient, written and oral, regarding the importance of following a daily schedule is the gold standard for fostering adherence. A personalized drug schedule that includes a matrix of activities of daily living can be devised into which drug schedules can fit. Critical to that plan is inclusion of any changes that occur at the time of hospital discharge. This time routinely creates confusion as to what is still on the active plan and what has changed (Brieger et al, 2018).

Simplifying the Complexity of the Regimen

The more complex the medication regimen, the less likely the patient is to adhere to taking their medications (Pantuzza et al, 2017; Wakai et al, 2021). Simplification of the regimen, including fixed-dose combination into single tablets and once-daily dosing, increases adherence (Elnaem et al, 2020; Parati et al, 2021). Combining simplification strategies improves adherence and clinical outcomes (Elnaem et al, 2020).

Sensory or Mobility Challenges

Patients need to be able to read the label and open pill bottles to easily self-administer medications. Large-print labels can increase safety for those with visual impairment. Prescribers need to anticipate sensory or mobility problems and offer solutions, such as easy-open containers. Prescribers and patients must also address any safety plans required when ease of access

increases risks of inadvertent use by other members of the household and guests.

Cues as Reminders

Multiple methods can be employed to provide cues to remember to take medications. Some patients use a simple visual cue, such as putting their morning medication near the coffee pot to remind themselves to take their medication when they make the coffee. Pill containers can be purchased with compartments from once-daily to multiple times per day dosing and from weekly to monthly schedules. These containers not only serve as cues to take a drug but also help to monitor when a drug is or is not taken. Daily calendars with sections for each hour of the day can be marked with the name of the drug to be taken with stickers to indicate dosing completion. Building cues for remembering to take medications into daily routines can be taught to patients, as in the SystemCHANGE study, and improves adherence (Whittington et al, 2022).

Scheduling Visits for Medication Follow-Up

Patients who miss appointments are often those who need the most help in improving their ability to adhere to a drug regimen. Such patients often benefit from clinical scheduling that matches their drug regimen. If a drug is prescribed for 2 weeks, the next appointment should be on the day after the drug should be completed. For chronic illness, clinic scheduling around the time for any laboratory work or doing physical assessments such as blood pressure can also include consideration for the time to fill the prescriptions.

One-stop shopping for medical care and prescription refills may improve adherence. Larger clinics with on-site pharmacies or even pharmacy-based convenient care clinics may provide the bonus of overcoming barriers to filling and refilling medications.

Financial Effects

Cost can have an impact on the ability and willingness of the patient to adhere to drug regimens. Basic needs (e.g., food, housing) may take precedence over drugs in planning a monthly budget. Patients who cut back on their prescriptions because of cost are 75% more likely to suffer a significant decline in their overall health, with 50% more likely to have had

a heart attack, stroke, or chest pain episode than those who filled their prescriptions.

Prescribers should keep contact information on hand for large pharmaceutical companies that offer coupon reductions and home-delivery options. Many companies have need-based programs that result in no-cost medications for patients in temporary or even permanent financial crisis. During times of disaster, larger pharmacy chains provide rapid refills and low-cost substitutes for medications lost during floods, fires, and windstorms.

Measuring Adherence

Adherence can rarely be measured by only one method. Methods that may be used include patient reports, clinical outcomes, pill counts, refill records, and medication adherence tools. Specific suggestions are listed in Table 1–3.

Patient Reports

Patient reports are the easiest monitoring tool, but use caution when determining whether the patient is actually pseudocompliant, telling the provider what the provider wants to hear rather than revealing the reality of nonadherence. Patients do not want to be scolded or chastised when nonadherence is discovered. Asking the "why" behind not taking medications helps to understand previously unknown or new barriers to adherence. Ask if there are things that can be done to help overcome the barriers to success.

Table 1–3 Measuring Adherence

Measurement Type	Examples
Patient reports such as drug diary with daily logs of dose taken and refills obtained	Record daily dosing and associated home testing such as blood sugars or weights.
Clinical outcomes	Track trend in status such as lowered blood pressure, weight charts, and laboratory markers such as HbA_{1c}.
Pill counts	Patients bring in bottles or bubble packs. Newer containers count delivery of inhalations and times bottle is opened.
Refill records	Records of refills from pharmacies and via calls to triage nurse monitor timing of use or overuse.

Medication Adherence Scales

There are several medication adherence scales in the literature; however, none is considered the gold standard. A review of four common scales is a good starting point (Culig & Leppee, 2014; Lavsa et al, 2011). The fastest to administer is the Medication Adherence Questionnaire (MAQ, also known as the Morisky 4), which is presented in Box 1–2. Because there are few questions and it is very easy to score, it is a popular tool to try to get to the source of adherence issues, including adverse drug effects and memory issues. The psychometrics include a reliability coefficient of $\alpha = 0.61$ (Lavsa et al, 2011). The addition of measuring self-efficacy is found in the Self-Efficacy for Appropriate Medication Use Scale (SEAMS) (Lamarche et al, 2018). Both the MAQ and the SEAMS have been validated in low-literacy populations.

BOX 1–2 MORISKY SIMPLIFIED SELF-REPORT MEASURE OF ADHERENCE

Scoring: 0 = High Adherence; 1–2 = Medium Adherence; 3–4 = Low Adherence

1. Do you ever forget to take your medicine?
2. Are you careless at times about taking your medicine?
3. When you feel better, do you sometimes stop taking your medicine?
4. Sometimes if you feel worse when you take your medication, do you stop taking it?

Adapted from Jani, A. A., Stewart, A., Nolen, R. D., & Tavel, L. (2002). Medication adherence and patient education. Florida AIDS Education & Training Center. In *HIV/AIDS primary care guide* (p. 87). Gainesville, FL: University of Florida Press.

Predictors of Adherence

Multiple factors affect medication adherence, as outlined in Table 1–4. Additional elements that may influence adherence include the personal elements of self-efficacy or health beliefs, and biomedical influences such as functional impact of the disease. Each individual patient has unique elements that influence adherence to varying degrees at different points of time (Fig. 1–1).

The elements that influence adherence may be grouped into spheres of influence with elements of potential positive and/or negative contribution within those spheres (Robinson, 2016). Determining which factors are affecting adherence at any point in time requires the advanced practice prescriber to assemble a complete nursing database of the elements that are playing into the current picture of adherence. These influences are not static; the elements are constantly in motion, with the importance of particular spheres of influence or several elements coming and going in duration and degree of impact on adherence to the therapeutic regimen. Every sphere plays a role in every patient's choices, abilities, and capabilities for self-care. A particular sphere or factor that may have played a key role previously can become more or less powerful in its influence. When previously reliable prescription adherence changes, the prescriber in tandem with the patient must return to the database to determine what new spheres and elements of influence might be at work.

Providers are encouraged to consider social factors and financial and health system factors when planning treatments in concert with patients. Planning must go beyond the disease factors that direct selection of therapeutic agents based on standard severity and degree of complexity of

physiological effects. In concordance with the patient, the prescriber must weigh the pros and cons of different options, regimen complexity, and any concurrent medication or lifestyle challenges that may influence the patient's ability to adhere to the regimen. Predicting potential issues and exploring methods to overcome any objections are critical to promoting adherence because trust and methods to improve patient motivation are keys to success (Young et al, 2017).

Table 1– Factors Influencing Adherence 4

General Health Status	Medical History, Nutritional Assessment, and Comorbidities
Life goals	To understand deeper issues, such as the following: • What gives meaning to a patient's life • The context of illness and treatment in a patient's life • The patient's definition of quality of life • A patient's attitudes and motivations based on their self-perception
Medication history	Past experience, current regimens, and side effects from all medications
Comorbidities	Psychiatric, substance use, and medical illnesses
Social stability	Housing status, food resources, transportation needs, financial status, and insurance status
Employment status	Type of job, constraints, and disclosure issues
Health beliefs and cultural background	Language and perceptions toward illness and chronic illness, diagnosis, prognosis, role of medications, understanding of consequences of medication nonadherence, and spiritual/religious orientation in reference to one's life and health goals
Family and social support	Identification of personalized medication facilitator and network of social support
Educational background	Educational level, literacy level, baseline knowledge regarding specific chronic illness, medications, and importance of adherence

Adapted from Jani, A. A., Stewart, A., Nolen, R. D., & Tavel, L. (2002). Medication adherence and patient education. Florida AIDS Education & Training Center. In *HIV/AIDS primary care guide* (p. 86). Gainesville, FL: University of Florida Press.

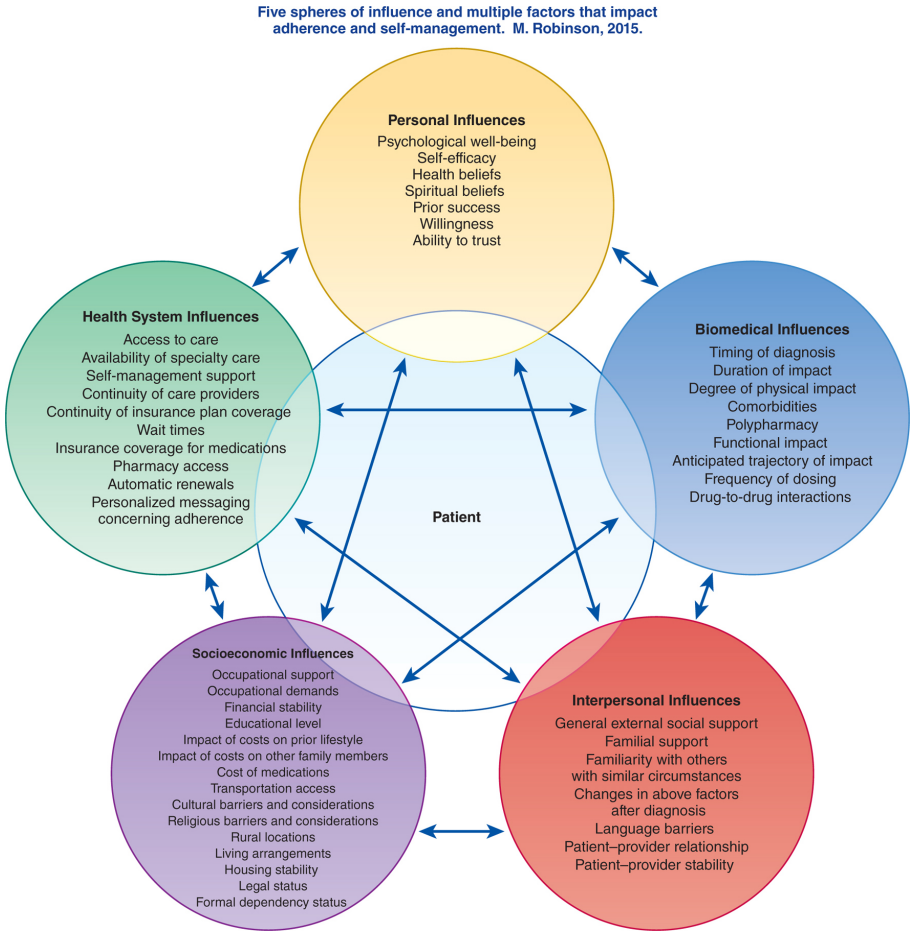

Figure 1–1. Five spheres of influence and multiple factors that affect adherence and self-management. *Robinson, M. (2015). Derived from Wheeler, K. J., Roberts, M. E., & Neiheisel, M. B. (2014). Medication adherence part two: Predictors of nonadherence and adherence.* Journal of the American Association of Nurse Practitioners, 26*(4), 225–232.*

REFERENCES

American Association of Nurse Practitioners. (2023). Practice Environment by State. https://www.aanp.org/advocacy/state/state-practice-environment

American Medical Association. (2023). *Advocacy issue briefs.* https://www.ama-assn.org/health-care-advocacy/advocacy-update

Brieger, D., Chow, C., Gullick, J., Hyun, K., D'Souza, M., Briffa, T., & CONCORDANCE Investigators. (2018). Improving patient adherence to secondary prevention medications 6 months after an acute coronary syndrome: Observational cohort study. *Internal Medicine Journal, 48*(5), 541–549. https://doi.org/10.1111/imj.13736

Brody, J. (2017, April 17). The cost of not taking your medicine. *The New York Times,* p. D7. https://www.nytimes.com/2017/04/17/well/the-cost-of-not-taking-your-medicine.html

Cahaya, N., Kristina, S. A., Widayanti, A. W., & Green, J. (2022). Interventions to improve medication adherence in people with schizophrenia: A systematic review. *Patient Preference and Adherence, 16,* 2431–2449. https://doi.org/10.2147/PPA.S378951

Canadian Institute for Health Information. (2023). *Nurse practitioners*. https://www.cihi.ca/en/nurse-practitioners

Canadian Nurses Association. (2019). *Advanced practice nursing: A pan-Canadian framework.* https://www.cna-aiic.ca/en/nursing/advanced-nursing-practice

Center for Disease Control and Prevention (CDC). (2023). *CDC Clear Communication Index*. https://www.cdc.gov/ccindex/

Chun-Yun Kang, G. (2022). Technology-based interventions to improve adherence to antihypertensive medications—An evidence-based review. *Digit Health, 8,* 20552076221089725. http://doi.org/10.1177/20552076221089725

Culig, J., & Leppee, M. (2014). From Morisky to Hill-Bone; self-reports scales for measuring adherence to medication. *Collegium Antropologicum, 38*(1), 55–62.

Elnaem, M. H., Irwan, N. A., Abubakar, U., Syed Sulaiman, S. A., Elrggal, M. E., & Cheema, E. (2020). Impact of medication regimen simplification on medication adherence and clinical outcomes in patients with long-term medical conditions. *Patient Preference and Adherence, 14,* 2135–2145. https://doi.org/10.2147/PPA.S268499

Fortuna, R. J., Nagel, A. K., Rocco, T. A., Legette-Sobers, S., & Quigley, D. D. (2018). Patient experience with care and its association with adherence to hypertension medications. *American Journal of Hypertension, 31*(3), 340–345. https://doi.org/10.1093/ajh/hpx200

Goldsmith, L. J., Kolhatkar, A., Popowich, D., Holbrook, A. M., Morgan, S. G., & Law, M. R. (2017). Understanding the patient experience of cost-related non-adherence to prescription medications through typology development and application. *Social Science & Medicine, 194,* 51–59. https://doi.org/10.1016/j.socscimed.2017.10.007

Hoskins, K., Ulrich, C. M., Shinnick, J., & Buttenheim, A. M. (2019). Acceptability of financial incentives for health-related behavior change: An updated systematic review. *Preventive Medicine, 126,* 105762. https://doi.org/10.1016/j.ypmed.2019.105762

Institute of Medicine. (2010). *The future of nursing: Leading change, advancing health*. Washington, DC: National Academies Press. http://www.nationalacademies.org/hmd/Reports/2010/The-Future-of-Nursing-Leading-Change-Advancing-Health.aspx

Islam, S. M. S., Mishra, V., Siddiqui, M. U., Moses, J. C., Adibi, S., Nguyen, L., & Wickramasinghe, N. (2022). Smartphone apps for diabetes medication adherence: Systematic review. *JMIR Diabetes, 7*(2), e33264. https://doi.org/10.2196/33264

Lamarche, L., Tejpal, A., & Mangin, D. (2018). Self-efficacy for medication management: A systematic review of instruments. *Patient Preference and Adherence, 20*(12), 1279–1287. https://doi.org/10.2147/PPA.S165749

Lavsa, S. M., Holzworth, A., & Ansani, N. T. (2011). Selection of a validated scale for measuring medication adherence. *Journal of the American Pharmacists Association, 51*(1), 90–94.

Luthy, K., Peterson, N., & Wilkinson, J. (2008). Cost-efficient treatment options for uninsured or underinsured patients for five common conditions. *Journal for Nurse Practitioners, 4*(8), 577–584.

Lyles, C. R., Sarkar, U., Schillinger, D., Ralston, J. D., Allen, J. Y., Nguyen, R., & Karter, A. J. (2016). Refilling medications through an online patient portal: Consistent improvements in adherence across racial/ethnic groups. *Journal of the American Medical Informatics Association, 23*(e1), e28–33. https://doi.org/10.1093/jamia/ocv126

National Academies of Sciences, Engineering, and Medicine. (2021). *The future of nursing 2020–2030: Charting a path to achieve health equity.* Washington, DC: The National Academies Press. https://doi.org/10.17226/25982

National Council of State Boards of Nursing. (2018). Independent prescribing—CNP. https://www.ncsbn.org/cps/rde/xchg/SID-26577D22-43187C84/ncsbn/hs.xsl/5411.html

Neiman, A. B., Ruppar, T., Ho, M., Garber, L., Weidle, P. J., Hong, Y., … Thorpe, P. G. (2017). CDC Grand Rounds: Improving medication adherence for chronic disease management—Innovations and opportunities. *MMWR Morbidity and Mortality Weekly Report, 66*(45), 1248–1251. http://dx.doi.org/10.15585/mmwr.mm6645a2

Pantuzza, L. L., Ceccato, M. D. G. B., Silveira, M. R., Junqueira, L. M. R., & Reis, A. M. M. (2017). Association between medication regimen complexity and pharmacotherapy adherence: A systematic review. *European Journal of Clinical Pharmacology, 73*(11), 1475–1489. https://doi.org/10.1007/s00228-017-2315-2

Parati, G., Kjeldsen, S., Coca, A., Cushman, W. C., & Wang, J. (2021). Adherence to single-pill versus free-equivalent combination therapy in hypertension: A systematic review and meta-analysis. *Hypertension, 77*(2), 692–705. https://doi.org/10.1161/HYPERTENSIONAHA.120.15781

Robinson, M. (2016). Five spheres of influence and multiple factors that impact adherence and self-management. In T. Woo & M. Robinson (Eds.), *Pharmacotherapeutics for advanced nurse prescribers*. Philadelphia: F.A. Davis.

Sakraida, T. J., & Robinson, M. V. (2009). Health literacy self-management by patients with T2DM and stage 3 CKD. *Western Journal of Nursing Research, 31*(5), 627–647. https://doi.org/10.1177/0193945909334096

Sarver, N., & Murphy, K. (2009). Management of asthma: New approaches to establishing control. *Journal of the American Academy of Nurse Practitioners, 21*(1), 54–65. http://jpp.sagepub.com/content/early/2013/07/04/0897190013493806

Simon, E., Edwards, A. M., Sajatovic, M., Jain, N., Montoya, J. L., & Levin, J. B. (2022). Systematic literature review of text messaging interventions to promote medication adherence among people with serious mental illness. *Psychiatric Services (Washington, D.C.), 73*(10), 1153–1164. https://doi.org/10.1176/appi.ps.202100634

Taub, S., Krivoy, A., Whiskey, E., & Shergill, S. S. (2022) New approaches to antipsychotic medication adherence—Safety, tolerability and acceptability. *Expert Opinion on Drug Safety, 21*(4), 517–524. https://doi.org/10.1080/14740338.2021.1983540

U.S. Food and Drug Administration. (2016). *Special feature: Why you need to take your medications as prescribed or instructed.* https://www.fda.gov/drugs/special-features/why-you-need-take-your-medications-prescribed-or-instructed

U.S. Food and Drug Administration, Center for Drug Evaluation and Research. (2023). *Advancing health through innovation: New drug therapy approvals 2022*. https://www.fda.gov/drugs/new-drugs-fda-cders-new-molecular-entities-and-new-therapeutic-biological-products/new-drug-therapy-approvals-2022

Wakai, E., Ikemura, K., Kato, C., & Okuda, M. (2021). Effect of number of medications and complexity of regimens on medication adherence and blood pressure management in hospitalized patients with hypertension. *PLoS ONE, 16*(6), e0252944. https://doi.org/10.1371/journal.pone.0252944

Wheeler, K., Roberts, M., & Neiheisel, M. (2014). Medication adherence part two: Predictors of nonadherence and adherence. *Journal of the American Association of Nurse Practitioners, 26*(4), 225–232. https://doi.org/10.1002/2327-6924.12105

Whittington, M., Goggin, K., Noel-MacDonnell, J., Hathaway, D., Remy, L., Aholt, D., … Russell, C. (2022). Cost-effectiveness analysis: Personal systems approach in improving medication adherence in adult kidney transplant patients. *Journal for Healthcare Quality, 44*(4), 240–252. https://doi.org/10.1097/JHQ.0000000000000327

Yalçin, N., Ak, S., Gürel, Ş. C., & Çeliker, A. (2019). Compliance in schizophrenia spectrum disorders: The role of clinical pharmacist. *International Clinical Psychopharmacology, 34*(6),

298–304.
Young, H. N., Len-Rios, M. E., Brown, R., Moreno, M. M., & Cox, E. (2017). How does patient–provider communication influence adherence to asthma medications? *Patient Education and Counseling, 100*(4), 696–702. https://doi.org/10.1016/j.pec.2016.11.022

CHAPTER 2

REVIEW OF BASIC PRINCIPLES OF PHARMACOLOGY

Peter J. Rice

PHARMACOLOGY—THE STUDY OF DRUGS

Pharmacology is the study of drugs and their actions. Pharmacologists, those who study drugs and their actions, consider a drug to be any chemical substance that produces a measurable biological response. Drugs include not only prescription medications but also nonprescription medications, botanicals, drugs of abuse, and poisons.

As we consider the variety of drugs and the measurable responses they produce, it will be helpful to think about what we would like to see in an ideal drug (Box 2–1). There are no perfect drugs—yet. But defining what would make an ideal drug will help us understand how medicines have developed over time and what properties to consider as we compare drugs to choose the best medication for an individual patient.

HOW NEW DRUGS ARE DEVELOPED

Pharmaceutical companies develop drugs to help patients and to make money. The early part of the drug development process is called the *preclinical stage.* Identification of promising drugs and testing in animals occur during this stage. Pharmaceutical companies will identify a drug target, starting sometimes with ingredients isolated from a plant (or an organism in the case of antibiotics) that has desirable medicinal properties, sometimes with a molecular target identified in the body to produce the desired response, and sometimes with a disease in need of treatment. It is

common for companies to enlist medicinal chemists, who specialize in designing and synthesizing new drugs. Medicinal chemists can provide many new chemical compounds for the preclinical process. Each drug might have a small difference in its chemical structure that will change its drug properties. Many drugs are examined as pharmaceutical companies seek the elusive perfect drug with just the right combination of properties. Preclinical studies are performed on cells, on isolated tissues and organs, and in laboratory animals to identify promising compounds and establish their safety before human testing.

Drugs approved by the U.S. Food and Drug Administration (FDA) must be both safe and effective and are screened by pharmacologists specializing in various aspects of drug activity. Toxicologists specialize in understanding the harmful effects of drugs and predicting as early as possible in the development process if a drug will be likely to harm patients. Ideally, drugs will produce their desired effects at dosages well below the point of toxicity.

During the *clinical stage* of new drug development, pharmaceutical companies must establish the safety and effectiveness of new drugs in humans. Phase I clinical trials typically establish biological effects, as well as safe dosages and pharmacokinetics, in a small number of healthy patients. During phase II clinical trials, new drugs are used to treat disease in a small number of patients and establish the potential of the drug to improve patient outcomes. If the drug still looks promising, phase III clinical trials compare the new drug to standard therapy in a larger number of patients studied in populations across the country. New drugs must be at least as good as, and ideally better than, other available therapies. Throughout the process, pharmaceutical companies work with the FDA.

BOX 2– EXAMPLES OF GRADED RESPONSES TO DRUGS 2

- Blood pressure
- Heart rate
- Diuresis
- Bronchodilation
- Forced expiratory volume in 1 second (FEV_1)
- Pain (scale 1–10)
- Coma score

After being approved by the FDA, drugs are continuously monitored through postmarketing surveillance in which health professionals are encouraged to report adverse events, which are studied by both pharmaceutical companies and the FDA. During clinical trials, only several thousand patients receive a new drug. During the postmarketing period, a larger population of patients receives the drug, sometimes revealing additional adverse effects that occur less frequently with use of the drug.

Pharmacogenomics is the study of how patient variations in drug targets or metabolism affect drug therapy. Pharmacogenomic studies performed during the postmarketing phase can identify biological factors responsible for predictable beneficial or adverse effects in individual patients.

DRUG RESPONSES

Before a drug can produce a response, it often must overcome homeostasis, which is the tendency of a cell, tissue, or the body as a whole to maintain the internal environment by adjusting physiological processes. Drug effects depend on the amount of drug administered. If the dose is below that needed to overcome homeostatic mechanisms and produce a measurable biological effect, we see no response (Rice, 2014). If an adequate dose is administered, there will be a measurable biological response. With an even higher dose, we may see a greater response. At some point, however, we will be unwilling to increase the dosage further, either because we have already achieved a desired or maximum response or because we are concerned about producing additional responses that might harm the patient.

Because pharmacology is the study of substances that produce biological responses, measuring what happens when we administer drugs is important. We will need ways to express and compare drug activity so we can describe the action or effect of drugs, compare the effects of different drugs, and predict their pharmacological effects (Rice, 2014).

Dose–Response Curves

Drugs produce responses as a result of their chemical interactions with living systems. The relationship between the dose or concentration of a drug and its biological response follows the laws of chemistry. The law of

mass action defines chemical interactions and forms the theoretical foundation for drug responses that occur through receptors that moderate drug responses. Simply stated, the higher the concentration of a drug at its site of action, the more the drug will bind to its receptor and the greater the response will be. With a greater number of drug molecules in the vicinity, more are likely to interact with the receptor.

It is simplest to think that drug responses are directly related to the fraction of receptors that are occupied, or bound, by a drug. For example, 50% of the maximum response occurs at a blood level or concentration at which a drug occupies 50% of its receptors. But depending on the number of receptors in a tissue and the ability of drug binding to produce a change in the receptor conformation, far fewer receptors (less than 10%) may be needed to produce a maximum effect.

Types of Drug Responses

There are two basic types of drug responses: quantal and graded. These responses differ in how they are measured and how they dictate dosing decisions to achieve the desired effect.

Graded responses are biological effects that can be measured continually up to the maximum responding capacity of the biological system (Box 2–2). Most drug responses are graded. For example, changes in blood pressure are measured in millimeters of mercury (mm Hg), and patients may experience small or large changes in blood pressure following treatment with drugs. Graded responses are easier to manage clinically because we can see how each patient responds to a particular dose of medication and, if appropriate, alter the dosage to achieve a greater or lesser response. Thus, if a patient's blood pressure is too low or too high when a particular blood pressure medication is administered, we can adjust the dosage based on the patient's individual response.

BOX 2– IDEAL DRUG PROPERTIES 1

- Convenient route of administration, probably taken by mouth
- Established dosage
- Immediate onset of action
- Produces a single desired biological action
- Produces no unwanted effects

- Convenient duration of action
- Dosage unaffected by loss of kidney or liver function or by disease state
- Improves quality of life
- Prolongs patient survival

Quantal responses are effects that are either present or absent (Box 2–3). For example, seizures either occur or they do not. The same is true for pregnancy, rash, sleep, and death. Prediction of drug dosages or blood levels that produce quantal effects is much more reliable for a population of patients than for an individual patient. Data from a population of patients must be used to establish appropriate doses or blood levels to predict quantal effects in a large number of patients. For example, oral contraceptive doses are high enough to prevent pregnancy (a quantal response) in more than 99% of women. Note that even with anticonvulsants or oral contraceptives, we do not achieve a 100% response. Because of natural variation in drug metabolism and responses to drugs, there may always be individuals who fail to respond, even at higher dosages. In general, responses that are far outside the typical dose or concentration range occur in patients with unusual drug metabolism or receptor variations.

The distinction between graded and quantal responses is not always fixed. Certainly, patients are either pregnant or not and either dead or alive. However, for some other quantal responses such as seizures, we can also count the number of occurrences. This can be helpful in adjusting medications to improve patient response with fewer or shorter seizures (a graded response), even though the goal is for the patient to have no seizures (quantal response). We can also make graded responses quantal by considering such issues as, "Did drug therapy lower blood pressure to the target range?" or "How many patients had no headache?"

Expressing Drug Responses

Pharmacologists show the relationship between dosage or concentration and drug effect using graphs of the dose–response relationship, or dose–response curve. Graphs of drug responses will show the response on the vertical axis and the concentration or dose on the horizontal axis. And for statistical reasons, because drug dosages extend over a large range, the horizontal axis is logarithmic. This means that the graph covers a larger dosage range and that numbers are distributed along the axis so that moving

a certain distance right or left represents multiplying or dividing the dosage or blood level concentration by a fixed amount. Most dosage changes in patients are doubled or halved—a logarithmic adjustment.

BOX 2– EXAMPLES OF QUANTAL RESPONSES TO DRUGS 3

- Seizures
- Pregnancy
- Rash
- Sleep
- Death

Dose–response curves provide information on the relationship between dosage or concentration and responses for one or more drugs. To "read" a concentration–effect or dose–response curve, move from left to right along the horizontal axis; this represents an increasing dosage or concentration. At each dosage, the level of effect is shown by the vertical height of the curve. When concentration–response data are shown for two drugs or two responses on the same graph, we can compare the effects at each dosage level.

Pharmacologists compare drugs and their actions in several ways, including potency, efficacy, intrinsic activity, and selectivity. Potency is the expression of *how much* drug is needed to produce a biological response (Fig. 2–1). Potency describes the difference in concentration or dosage of different drugs required to produce a similar effect. Drugs that are more potent require a lower dosage or concentration to produce the same response as a higher dosage or concentration of a less potent drug. For example, compare doses of nonprescription drugs that relieve headache: 200 mg ibuprofen, 325 mg aspirin, and 50 mg ketoprofen. Because ketoprofen requires the lowest dose, it has the highest potency. Drugs that differ in potency differ in their horizontal position on the dose–response curve.

Efficacy is the expression of the *maximum effect* a drug can produce. For example, consider the treatment of pain. Many drugs will relieve mild pain. No matter how much we increase the dosage, drugs that work well for mild to moderate pain are usually ineffective for treating more severe pain, such

as cancer-related pain. Treatment of severe pain requires the use of stronger drugs, such as the opioid analgesics morphine or oxycodone. Morphine and oxycodone have higher efficacy for pain relief than ibuprofen. Drugs with high efficacy can produce greater effects than drugs with lower efficacy.

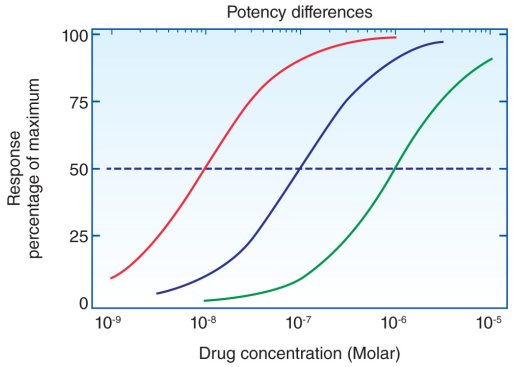

Figure 2–1. Concentration–effect curves for three drugs that differ in potency (i.e., the dose or concentration required to produce an effect). The drug concentration on the *x*-axis is expressed in molar units, representing the number of molecules in each liter of solution. The graded response is expressed as a percentage of maximum effect.

Intrinsic activity is very similar to efficacy in that it represents the ability of a drug to produce a large response. Intrinsic activity, however, describes the ability of a drug to produce a response once it has occupied specific receptors. Some drugs produce the maximum receptor stimulation once they occupy receptors; their response is limited by how many drug molecules occupy receptor sites. Other drugs with lower intrinsic activity can occupy the same number of receptors but will produce a lesser response. Drugs can also occupy receptors and produce no receptor stimulation; they merely block the action of neurotransmitters or other drugs.

Drug Selectivity

In clinical use, drugs produce both desired and undesired responses. Of course, we should be administering drugs with a goal in mind, which should include a level of response, either graded or quantal. The level of undesired response we are willing to accept typically depends on what we are treating and the type of adverse effect. Patients regularly accept all kinds of adverse

effects from cancer chemotherapy when their lives are on the line. Patients with cancer tolerate hair loss, nausea, vomiting, and generally feeling miserable because those adverse effects result from killing cancer cells. Sometimes patients make surprising decisions regarding drugs that produce both desirable and undesirable effects. For example, some patients will live in severe pain rather than take an analgesic that causes constipation or sedation. For hypertension and other symptomless disease states, patients are often reluctant to accept even minor adverse effects. Patients receiving pharmacotherapy present the opportunity and challenge to adjust medications and dosages to achieve optimal results with minimal adverse effects and educate patients to continue therapy even if minor adverse effects occur.

There are challenges to expressing drug selectivity. The most reasonable way to express selectivity is as a ratio of the dose or concentration producing the undesired effect to the dose or concentration producing the desired effect. This is the same as determining how many times the therapeutic dosage needs to be increased to produce the undesired effect. A medication that produces the desired response at a dose of one tablet and does not produce undesirable effects unless five tablets are administered has a selectivity ratio of 5. That is not a bad drug. But many drugs produce significant undesired effects at or slightly above the therapeutic dosage.

It would be preferable to describe drug selectivity in a way that encourages optimal drug use. A medication that has high selectivity and produces only the desired effects clearly would be the treatment of choice. There are problems, however, with consistently expressing selectivity based on desired and undesired effects. Medications often have more than one effect and might be used for any of their effects, so sometimes a particular effect is desired and sometimes it is undesired. Diphenhydramine can be a very beneficial drug that is used as an antipruritic for itching, an antihistamine for allergies, an anticholinergic that dries secretions, and a sleeping aid that produces drowsiness. Desired and undesired effects can differ for each patient, and if we compare dosages, there are several selectivity ratios.

The therapeutic index is a special ratio describing drug selectivity. It is the ratio of the lethal dose to the therapeutic dose of a drug. There are some limitations to the therapeutic index: It uses death, a very unacceptable adverse effect, and it uses data from animal studies. But the therapeutic

index provides a fixed comparison for drug safety. The therapeutic index of drugs on the market is, of course, always greater than 1; a therapeutic index of less than 1 means that the drug kills before it cures. The therapeutic index ranges from 2 for some drugs (cancer chemotherapy, lithium carbonate) to 6,000 for others (penicillin in nonallergic patients).

Drug Responses in the Real World

Pharmacotherapy in real patients is different than what has been described. The placebo effect is a pharmacological effect that is not caused by the active ingredient. Placebos are tablets or capsules that contain no active ingredient; they are sometimes called "sugar pills" because they used to be filled with sugar. It is common for drug studies to have a placebo group to see whether patients are responding to the active drug or just to the act of taking a medication (Fig. 2–2). The placebo group will also be monitored for adverse effects, which establishes the level in untreated patients. Placebo effects are relatively high in some disease states, such as depression, and very low in other disease states, such as cancer.

Dose–effect relationships in the real world do not start at zero response; they start at the response associated with the placebo effect. The level of response increases as the dose increases but rarely reaches 100%. Instead, the risk of toxicity will limit the maximum dosage, or another drug will be used if there has not been a satisfactory effect.

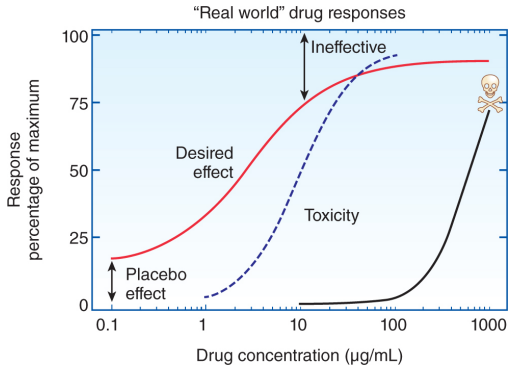

Figure 2–2. Theoretical representation of how drugs produce effects in clinical practice. Drug concentration (*x*-axis) increases from left to right. Some patients will respond at low dosages, either because of the placebo effect or sensitivity to the drug. As drug concentrations increase, greater numbers of patients will respond favorably, but some will also respond adversely. At some dosage or concentration, the presence of toxic effects precludes the use of higher doses in patients.

Brand Versus Generic Drugs

New drugs are patented to protect the innovator company for a period during which only it can manufacture the drug. New drugs are given a generic name that anyone can use to market the drug, but innovator companies will create a brand name that only they can use. During the years after a drug is released, it is marketed under the brand name, and patients and practitioners often become familiar with the product under its brand name. Once the patent on the original drug expires, other companies can manufacture generic products that are designed to imitate the brand-name product. Once competition is allowed, generic manufacturers formulate similar dosage forms with the same active ingredient in the same amount as the branded product.

Patients often wonder about the relationship between the effects of brand-name and generic preparations. Because brand-name and generic preparations contain the same active ingredient, the body treats the two exactly the same. Differences between brand-name and generic preparations can occur in the inactive ingredients of the tablet or capsule, such as coloring or filler materials.

Generic products are *supposed* to provide patients with the same dosage as brand-name products. Differences between brand-name and generic formulations result from variations in the time it takes for the formulations to break apart in the stomach and dissolve before absorption. There are always differences in the speed, or rate, of absorption. The FDA rates generic formulations in its *Orange Book,* and products with an AB rating are considered to be similar enough to use as generic substitutes for brand-name products.

Brand-name and generic preparations in which the drug is already in solution, such as injectables, are always similar in their rate and extent of absorption.

RECEPTORS

We can think of drug responses in a simple way. A favorite cartoon shows a mathematician solving a problem. The solution begins with an equation that states the problem, and a gap follows in which the mathematician writes "and then a miracle happens," followed by the result. If we choose to think of drug responses as the predictable miracles that follow drug administration, then pharmacology would be no more than memorizing which responses go along with which drugs. A century ago, medical schools and pharmacy schools had departments of *materia medica,* a Latin way to describe the pairing of a drug with a response without necessarily knowing what happens in between. Today, we encounter the same knowledge level for many botanicals, and patients and health professionals alike will often consult manuals that list symptoms to be treated and the plant product that can produce the desired action.

If we choose to understand drug action and why drugs produce predictable sets of responses, we need to look at the biological molecules and the chemical principles that underlie responses to drugs. Almost all drugs act through receptors. Receptors are the large molecules, usually proteins, that interact with and mediate the action of drugs. Receptors are important because they determine the relationship between dose and effect, the selectivity of drugs, and the actions of pharmacological antagonists.

Pharmacologists tend to categorize drug activity based on the receptors through which individual drugs act. There are several benefits to organizing the study of pharmacology around receptors. It simplifies the amount of

material that needs to be memorized. Receptors provide a theoretical framework for understanding and predicting drug actions and the relationship between dose (or concentration) and effect. Also, receptors within the same "superfamily" often share properties.

Drug targets include enzymes, ion channels, cell surface receptors, nuclear hormone receptors, transporters, and DNA. In each case, chemical interactions take place between drug and receptor molecules. Receptors act through a number of mechanisms, including those described in the following sections. Chemical energy from the drug–receptor interaction is used to change the receptor in some way that alters physiological processes to produce cellular changes that result in a measurable response.

Because chemical interactions determine the activity of a drug at a particular receptor type, changes in chemical structure result in changes in pharmacological activity. The correlation of chemical structure with pharmacological activity is called the *structure–activity relationship* (SAR). SARs can be helpful in understanding receptors and for developing new drugs. There are separate, independent SARs for different drug properties (e.g., potency, selectivity, toxicity), so the fact that any one drug property changes for the better (or worse) does not necessarily mean that the change affects the other properties of the drug.

Ion Channel Receptors

Ion channel receptors transmit signals across the cell membrane by increasing the flow of ions and altering the electrical potential or separation of charged ions across the membrane. Ion channel receptors can produce responses with rapid onset and short duration. For example, activation of ion channels by nicotinic receptors causes muscle contraction. Muscle movement must start immediately and stop at will to be effective. The nicotinic receptor consists of five subunits, which form a cylindrical structure with a hole in the center. When acetylcholine (ACh) binds to the two alpha subunits, a conformational change occurs, which momentarily opens the central channel, permitting sodium to enter and potassium to leave the cell (Fig. 2–3). Two binding sites for ACh result in a steep concentration–effect curve, so a very small change in ACh concentration at the neuromuscular junction will produce dramatic openings in ion channels. Notice that the two ACh sites are a certain distance apart. This is important for the SAR of drugs that block nicotinic receptor sites.

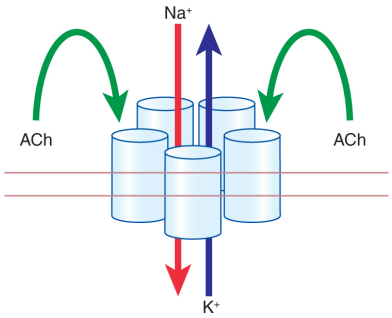

Figure 2–3. The nicotinic acetylcholine (ACh) receptor comprises five subunits that come together to form an ion channel receptor. When ACh binds to two sites on the receptor, the ion channel opens to let sodium (Na^+) and potassium (K^+) cross the cell membrane to initiate a response.

Ion channel receptors include receptors for ACh (nicotinic), gamma-aminobutyric acid (GABA), and excitatory amino acids (glycine, aspartate, glutamate, etc.).

Receptors Coupled to G Proteins

Several guanine nucleotide regulatory proteins (or G proteins) are present in cell membranes. G proteins share a similar structure in which seven regions of protein span the cell membrane to create a pocket (in which drugs can bind) and end with a receptor "tail" inside the cell (Fig. 2–4). Individual G-protein receptors have the general G-protein structure but differ in their *binding site,* the area that recognizes and binds to drugs, and in the intracellular portions of the G protein that control what happens after a drug is bound. Receptors are activated when specific drugs interact with the binding site, producing a conformational change, a sort of twist, in the G protein. Receptor activation then produces intracellular changes in the binding of the G-protein receptor to other proteins that control response through other molecules called *second messengers.*

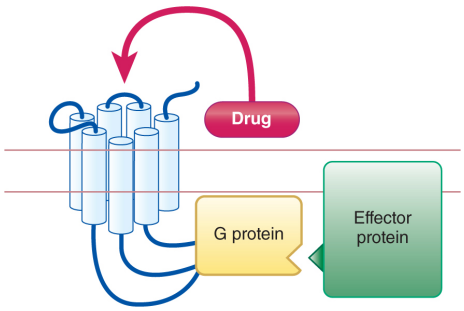

Figure 2–4. G-protein–coupled receptors are proteins that cross the cell membrane seven times, creating a pocket in which drugs can interact. Bound drugs may stimulate the receptor to release a G protein that can interact with various effector proteins to produce physiological responses.

Second messengers include molecules such as cyclic adenosine monophosphate (cAMP), Ca^{++}, phosphoinositides, and diacylglycerols; each can be produced as a result of stimulating different G-protein–linked receptors. The conformational change in the G-protein receptor can also make intracellular parts of the receptor available for enzymes to phosphorylate. Phosphorylation, placing a phosphate group on a protein, is a way of marking it for activation or inactivation.

G proteins are made up of three major subunits (alpha α, beta [β], and gamma γ). Minor variations (isotypes) of each subunit can result in a great deal of variation in G proteins just from different combinations of alpha, beta, and gamma subunits. Variations in G-protein subunits and receptors allow them to interact with a variety of drugs and produce different responses depending on which drug is recognized by the receptor, which subunits are involved, and which effector protein is altered. Individual cells and tissues can produce various types and amounts of G proteins (Kenakin, 2005). This is a homeostatic mechanism used by the body to adapt to disease states and drug treatment.

Receptors coupled to G proteins mediate the level of second messengers following the extracellular interaction of the drug with the receptor. This receptor superfamily includes a large number of receptors that recognize different drugs and activate or inhibit different second messengers. For example, beta-adrenoceptors mediate the effects of epinephrine (also called *adrenaline*) on the heart and make it beat faster and stronger at scary movies.

In the prototype beta-adrenoceptor system, interaction of epinephrine with the receptor replaces guanosinediphosphate (GDP) with guanosine triphosphate (GTP), activating the G protein. The G protein uncouples from the receptor and stimulates the enzyme adenylyl cyclase to generate the intracellular second messenger cAMP. Intracellular cAMP produces a pharmacological effect, such as making the heart beat stronger and faster, until the cAMP breaks down. Caffeine produces similar effects by inhibiting the breakdown of cAMP.

Changes in the number of receptors alter responsiveness to drugs. The number of available G-protein receptors decreases when the receptors are stimulated. Receptors in the cell membrane are phosphorylated at specific intracellular sites, which can lead to desensitization or loss of receptors or responsiveness following receptor activation. These receptor changes influence drug treatment by limiting the time in which certain drugs can be used clinically and by placing patients at risk for rebound effects when certain drugs are discontinued.

Transmembrane Receptors

Transmembrane receptors consist of an extracellular hormone-binding domain and an intracellular enzyme domain that phosphorylates the amino acid tyrosine. When an active hormone binds to the extracellular binding site, the receptor conformation changes and two receptors bind to each other, activating the enzyme and sustaining the effect (Fig. 2–5). Different receptors catalyze the phosphorylation of tyrosine residues on various downstream signaling proteins.

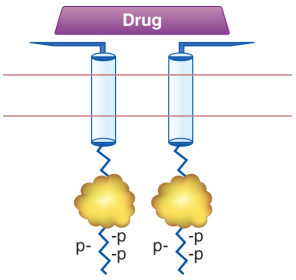

Figure 2–5. The insulin receptor is prototypical of tyrosine kinase receptors. These receptors are brought together by extracellular drug binding (insulin in the case of the insulin receptor), which activates the intracellular enzyme tyrosine kinase. Tyrosine kinase receptors activate one another by adding a phosphate ($-PO_4$) to select sites on cellular proteins, which in turn activates a physiological response.

The protein tyrosine kinase includes receptors for insulin, epidermal growth factor, and platelet-derived growth factor.

Intracellular Receptors Regulating Gene Expression

Lipid-soluble hormones can pass through the cell membrane and bind to intracellular receptors. The glucocorticoid receptor resides in the cytoplasm until it binds with a drug that has glucocorticoid activity. Binding of the drug displaces a stabilizing protein and permits the folding of the receptor into its active conformation. The receptor then moves to the nucleus, where it controls the transcription of genes by binding to specific DNA sequences (Fig. 2–6). Hormone receptors of this type include corticosteroids, mineralocorticoids, sex steroids, vitamin D, and thyroid hormones; these produce more sustained responses.

Enzymes

Enzymes are biological molecules that encourage specific chemical reactions in the body. For example, the enzyme acetylcholinesterase breaks a chemical bond in ACh to terminate its action and produce acetic acid and choline (Fig. 2–7). A different enzyme can reassemble these molecules back into ACh. Drugs can act to stimulate or inhibit specific enzymes. The anticoagulant heparin binds to the enzyme antithrombin-III and increases its inactivation of clotting factors. The anticholesterol statin drugs are inhibitors of the enzyme HMG-CoA (3-hydroxy-3-methyl-glutaryl

coenzyme A) reductase, which controls cholesterol synthesis in the body. Antibiotics are frequently inhibitors of enzymes essential for bacteria to remain alive.

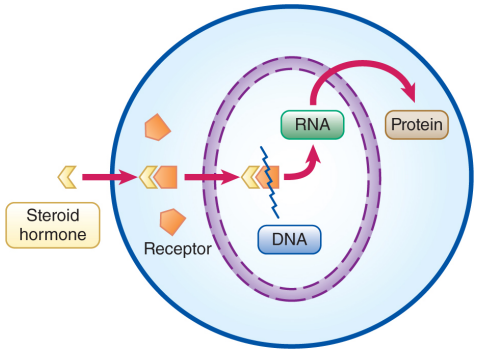

Figure 2–6. Steroid hormones diffuse through the cell membrane to interact with steroid receptors in the cytoplasm. The hormone–receptor pair relocates to the nucleus, where it can interact with DNA to effect RNA transcription and protein synthesis.

Drug Action at Receptors

Drugs can do three basic things once they bind to a receptor. Agonists, or full agonists, are drugs that produce receptor stimulation and a conformational change every time they bind. Full agonists do not need all of the available receptors to produce a maximum response. Some agonists can produce their maximum response by binding to less than 10% of the available receptors. The receptors that are left over and not needed for a response are called *spare receptors*.

Antagonists are drugs that occupy receptors without stimulating them. Antagonists occupy a receptor site and prevent other molecules, such as agonists, from occupying the same site and producing a response. Antagonists produce no direct response. The response we see following administration of antagonists results from their inhibition of receptor stimulation by agonists. For example, beta blockers such as propranolol and atenolol act as antagonists at the beta-adrenoceptor. Adrenergic nerve activity can raise heart rate, and patients with high heart rates experience a significant decrease in heart rate following administration of beta blockers. The same administration may have little effect on patients who lack adrenergic nerve activity and already have a lower heart rate. The effect of

antagonists depends on the background receptor activity that they can block.

Antagonists produce a shift in the concentration–effect relationship for agonists acting at the same specific receptor as the antagonist; they make agonists for that receptor appear less potent. The effect of an antagonist depends on its blood levels and its affinity for the receptor. Most antagonists in clinical use are competitive reversible antagonists, and it is possible to overcome the antagonist effects with higher concentrations of the competing agonist. A very small number of antagonist drugs (e.g., botulinum toxin, echothiophate, phenoxybenzamine) act by irreversibly binding to the receptor; their antagonism remains until the cell can produce new receptors.

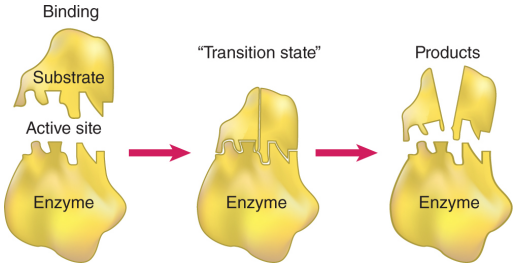

Figure 2–7. Enzymes bind to substrates and speed up biochemical reactions. Enzymes can serve as receptors to the substrate, which binds at the active site, or to drugs that control enzyme activity through binding at a different site.

Partial agonists are drugs that have properties between those of full agonists and antagonists. Partial agonists bind to receptors but when they occupy the receptor sites, they stimulate only some of the receptors so they can act as part agonist and part antagonist. This is sometimes called *intrinsic activity.* Partial agonists would require all of the available receptors to produce their full response, and the maximum response for a partial agonist is less than that for a full agonist. The beta blockers acebutolol, penbutolol, and pindolol are partial agonists. Administration of these drugs can block the effects of adrenergic nerves on heart rate, but partial agonist activity keeps heart rate from falling too low, as might occur following administration of a pure beta-adrenoceptor antagonist. Beta blockers with intrinsic sympathomimetic activity therefore control heart rate within a range higher than the response to an antagonist and lower than the response to an agonist.

Disease States and Receptors

Disease states or drug treatment can selectively alter the number of receptors in various tissues throughout the body. For example, hyperthyroidism upregulates, or increases, the number of beta-adrenoceptors, making hyperthyroid patients more likely to have hypertension and a rapid heart rate. Treatment with some agonist drugs can cause the receptors to downregulate, or decrease, in response to receptor stimulation; this can limit the duration over which the drug can be clinically useful. Treatment with some antagonist drugs can cause receptors to upregulate in response to the decrease in receptor stimulation, which can produce rebound effects if the antagonist is abruptly withdrawn.

Because the maximum response to partial agonists depends on the number of receptors, an increase in receptor number will increase the response to partial agonists.

Nonreceptor Mechanisms

Not all drugs act through receptors. General anesthetics, sodium bicarbonate (which neutralizes stomach acid), and chelating agents (which bind to and remove metal ions in the blood) are some examples of drugs with actions based on their physicochemical properties rather than interaction with receptors.

PHARMACOKINETICS

Pharmacokinetics is the branch of pharmacology dealing with the absorption, distribution through the body, metabolism, and excretion of drugs. Ideally, drugs will enter the body readily, go directly to their site of action, and have a favorable combination of metabolism and excretion that will make it easy to manage patients, even in the presence of kidney or liver disease.

Absorption

The way in which medications are presented to the body affects the speed, extent, and duration of drug absorption. The route of administration also affects patient adherence—that is, patients' willingness to follow recommendations for taking a medication (Box 2–4). For this reason, choosing the route of administration can have important implications for

drug therapy, and various routes of administration can be chosen based on the chemical properties of an individual drug, the condition of an individual patient, and the goal of drug treatment.

There is more to choosing the route of administration than just having medication enter the body. Patients can swallow a poorly formulated dosage form that travels through the intestines and arrives unchanged in the toilet. There is little biological effect from these "bedpan bullets" if the active medication never reaches its site of action.

Parenteral Administration

Medications may be administered parenterally (by injection) when immediate effect is required, when the active ingredients are destroyed or not absorbed by the gastrointestinal tract or other routes, or when the patient is unable to take an oral medication. A major limitation of parenteral administration is that it requires needles, syringes, and sterile technique.

Drug absorption is greatest for intravenous (IV) injection (Buxton & Benet, 2011). IV preparations consist of drugs that have been dissolved in aqueous solution and are sterile and ready to enter the bloodstream. Intramuscular or subcutaneous preparations may use drugs suspended in sterile media, which is usually aqueous but occasionally oil based. When administered by IV injection, all of the drug enters the bloodstream immediately. IV administration serves as the standard to which other routes of administration are compared when we consider *bioavailability,* which is the percentage of the administered drug that is absorbed. Although there are drawbacks to needles and the need for sterility, IV administration has the advantages of rapid or complete absorption and immediate drug action. A major disadvantage of IV administration is that once administered, the drug absorption cannot be slowed and the drug cannot be removed from the body. IV administration is common for emergency drugs and in the hospital setting.

Oral Administration

Oral administration is the most convenient and common route of administration. In contrast to IV administration, orally administered drugs must go through a number of steps on their way to the bloodstream (Buxton & Benet, 2011). Following oral administration, dosages in the form of tablets, capsules, or liquid make their way to the stomach and continue to move into and through the small and large intestines on their way to the

colon. Tablets or capsules must break apart and their drug contents must dissolve in stomach acid or intestinal fluid before the drug can be absorbed. This takes time, so orally administered drugs may not act as quickly as those administered via other routes. Orally administered drugs must pass through the lining of the intestines to enter the systemic circulation. Once absorbed, orally administered drugs travel to the liver, where they may be metabolized on their way to the bloodstream.

BOX 2– EFFECTS OF ROUTE OF ADMINISTRATION 4

- Compliance
- Bioavailability
- Onset of action
- Duration of action

Several related routes of administration overcome some of the barriers encountered with oral dosing. Sublingual administration (under the tongue) and buccal administration (between the cheek and gum, as with chewing tobacco) allow drugs to have a quicker onset of action and to avoid liver metabolism as they enter the bloodstream. For example, nitroglycerin sublingual tablets or sprays are used to treat chest pain. They can act within a minute or two and can help stop an anginal attack and avoid an emergency department visit. Buccal administration, although less common, is used with methyltestosterone and nicotine preparations.

Some medications are destroyed by stomach acid after oral administration or are absorbed too rapidly to be convenient. Enteric-coated formulations protect the medication in the stomach and only disintegrate and dissolve when they reach the less acidic conditions of the intestinal tract. Sustained-release preparations allow a drug to dissolve slowly in the intestines so the medication is absorbed over a period of time. It is important not to crush these preparations before administration because that would destroy the formulation and speed absorption, leading to higher blood levels of the medication than anticipated.

The use of oral medications may be limited when patients are nauseated, vomiting, or uncooperative (e.g., infants and children). Administration of suppository preparations into the rectum allows drug absorption that is

similar to oral administration. Although rectal administration is appropriate for some medications and is used for some pediatric medications, it is not universally acceptable to patients.

Site of Administration

Administration of medication close to where it will act has some notable theoretical advantages. When medications are administered near their site of action, higher concentrations may be achieved while minimizing unwanted effects in other parts of the body. Topical administration allows medication to be concentrated in the skin when patients need an anti-inflammatory (e.g., hydrocortisone) or an antifungal (e.g., clotrimazole) medication for a skin condition. This is particularly advantageous in that drugs pass more easily through damaged skin, so more drug is available to the areas of the skin that need the medication. Multidose inhalers and nebulizers are commonly used to administer drugs (e.g., albuterol) directly into the lungs. Ophthalmic preparations are sterile and suitable for administration to the eye. Because the eye is particularly sensitive, ophthalmic medications are typically buffered and isotonic so they do not cause discomfort when administered. Aural preparations, intended for administration into the ear canal, do not require the buffering and isotonicity of preparations for ophthalmic administration.

Bioavailability

Because not all of the administered dose may be dissolved, absorbed, or survive liver metabolism, only a fraction of an administered dose makes it to the bloodstream. The percentage of the administered dose that does enter the bloodstream is called the *bioavailability* of the dosage form. Bioavailability is 100% for parenteral administration but can range from less than 10% to more than 90% for oral administration (Buxton & Benet, 2011). When the bioavailability of an oral preparation is low, a higher dose will be given compared with an IV preparation, so the amounts reaching the bloodstream are similar. For example, an oral dose of 500 mg of ciprofloxacin can be substituted for a 400 mg IV dose; ciprofloxacin has about 80% oral bioavailability.

Peak Blood Levels

The speed at which drugs enter the bloodstream affects the maximum blood level that is achieved (Fig. 2–8). Rapid absorption leads to higher peak

blood levels, with a risk of greater toxicity and side effects. So rapid IV administration (e.g., "IV push") produces immediate drug effects but increases the risk of toxicity and adverse effects. For these reasons, some medications, such as aminoglycoside antibiotics, are administered by slow IV infusion over 30 to 60 minutes. This allows distribution to occur, keeps the blood level from getting too high, and minimizes toxicity.

Distribution

After a drug is absorbed, it still must reach its site of action to produce an effect. The process of drugs moving throughout the body is called *distribution.* Distribution of drugs can occur by transfer through the bloodstream and passive diffusion. Distribution can also be promoted or limited by the presence of transport systems that may selectively transport or exclude drugs based on size, charge, or chemical structure. Diffusion can influence the action of drugs because drugs can be effective only if they reach their site of action in adequate concentrations before metabolism.

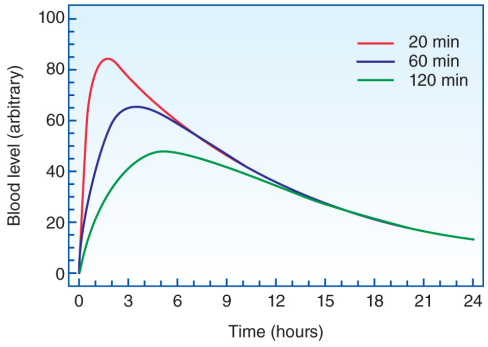

Figure 2–8. Blood levels for the same dose absorbed with peak times of 20 minutes, 60 minutes, or 120 minutes. Rapid absorption results in faster effect, but blood levels are higher with a greater likelihood of toxicity.

Properties That Affect Distribution

Drugs can passively diffuse most readily when they are small and uncharged and also have the right balance between water and lipid solubility (Buxton & Benet, 2011). Some of these properties will be related to the drug (e.g., molecular size and lipid:water solubility). Others will reflect drug properties as they present in an individual patient, such as pH, the acidity of the environment in which the drug finds itself. pH affects ionization of the drug. Of course, the drug may find itself in an acidic

environment (pH ~2) in the stomach and more neutral environments in the intestine (pH 6–8) and blood (pH 7.4). The patient's body will also be an environment that includes proteins to which the drug may bind.

Because passive diffusion represents transfer through partially permeable barriers, smaller molecules are better able to diffuse than larger molecules. Molecules with molecular weights of 500 or less are the best candidates for passive diffusion. Molecules with molecular weights greater than 5,000 are expected to diffuse poorly.

Henderson-Hasselbalch Relationship

Acidity is an important property of biological environments. Acidity is measured as pH, defined as $-\log[H^+]$; lower pH is more acidic. Normal pH in the body is around 7.4, and under conditions consistent with life, pH can range only about 0.3 units in either direction. Each 1 unit of pH change represents a 10-fold increase or decrease in the concentration of hydrogen ions, and each 0.3 pH unit change represents a 2-fold change in acidity.

Most drugs contain chemical functional groups, such as carboxylic acids and amines, that can exist in a neutral, uncharged form or in a charged form. The balance between the charged and uncharged forms depends on pH. At higher acidity (lower pH), carboxylic acid groups are uncharged, but amine groups are charged. At low acidity (higher pH under basic conditions), the amine groups are uncharged, but the carboxylic acid groups are charged. Each drug is unique, and the pH at which it exists half in the charged state and half in the uncharged state is defined as its acid dissociation constant or p*K*a.

It is an important principle in pharmacology that passive diffusion through biological barriers occurs most readily when drugs are in the uncharged state. Because the pH of body fluids is limited to a relatively narrow range and the p*K*a is a fixed property for an individual drug, we can calculate the percentage of charged and uncharged molecules for a drug at any pH if we know its p*K*a. The p*K*a can be an important property that influences the drug's absorption, distribution, and excretion.

Passive diffusion is a process through which drugs cross some type of biological barrier, such as a cell membrane or a layer of cells, based on the concentration difference between the two sides of the barrier. We would expect that passive diffusion would proceed until the concentration of drug is equal on both sides, but that is not quite what happens. Instead, passive

diffusion proceeds until the concentration of *un-ionized* drug is the same on both sides. As a result, pH differences can cause more drug to accumulate based on the fraction of un-ionized and ionized molecules. This is called *ion trapping.*

Protein Binding

Drugs passively diffuse and distribute when they are unbound and uncharged. Drugs can bind to various proteins present in the bloodstream, often called *plasma proteins.* Many plasma proteins are produced in the liver, and their presence in the blood reflects liver function, nutritional status, and the effect of aging and disease. Albumin is a major protein in the blood and is measured as part of a typical blood analysis. Albumin has a molecular weight of 66,500, which is too large to be excreted by the kidneys in healthy patients, although it is lost in the urine in renal disease. Other plasma proteins include alpha-1-acid glycoprotein, cortisol-binding globulin, sex hormone–binding globulin, and lipoproteins.

Binding to plasma proteins serves several important functions. Drugs bound to plasma proteins can freely circulate in the bloodstream rather than being distributed by passive diffusion from their site of absorption, so plasma protein binding helps normalize concentrations throughout the body (Buxton & Benet, 2011). Drugs that are bound to plasma proteins can be protected from metabolism in the liver and excretion by the kidneys, which can extend the period of time that drugs remain in the body.

Plasma proteins can be altered by disease states. Patients with poor nutrition may not have the protein building blocks to produce adequate amounts of plasma proteins. Patients with cancer can be undernourished as the cancer cells feed on the body. Patients with liver disease may lack the cellular function to produce one or more of the plasma proteins. Plasma proteins can also be affected by myocardial infarction, stress, and infection.

Plasma protein binding has advantages and disadvantages. As mentioned earlier, binding to plasma proteins can protect drugs from metabolism and excretion, extending the time the drugs remain in the body. But remember the general principle that drug action occurs through free, unbound drug. Protein binding, which may include binding to proteins that are not in the plasma, also prevents the interaction of drug molecules with their site of action. Plasma protein binding creates a reservoir of bound drug molecules

that can dissociate at any time to interact with drug receptors and produce responses.

Plasma protein binding encourages retention of the drug in the systemic circulation. Therefore, it may appear that blood levels of a drug are high, even if the drug is not at its active site. For example, when patients receiving digoxin, a cardiac glycoside used to slow and strengthen the heart, have clinical signs of toxicity and high blood levels, they can be given antibody fragments to digoxin (Digibind). The antibody fragments remain in the central circulation and bind to digoxin in the bloodstream, essentially pulling digoxin back into the bloodstream from its sites of action throughout the body. However, because digoxin is binding to its antibody in the bloodstream, its concentration rises even though there is much less free digoxin to produce pharmacological effects and toxicity. This illustrates how plasma protein binding holds drugs in the circulation and prevents their distribution to other sites in the body.

Binding to proteins is also the basis for a number of drug interactions. Drugs bound to plasma proteins cannot interact with their receptor. If a drug is very strongly bound to plasma proteins, then even a small change in the fraction that is bound can have significant pharmacological effects. Warfarin is an oral medication used to slow blood clotting in patients at risk for thrombosis. Warfarin is about 98% bound to plasma proteins, which means that only 2% of the drug is unbound and available to produce a pharmacological effect. What if the patient takes another drug that also binds to plasma proteins? If the binding of the second drug to plasma proteins displaces even a small fraction of warfarin, it can have a dramatic effect. If only an additional 2% of warfarin is displaced, for example, it would mean a doubling of circulating warfarin activity.

Transport Systems

Drug distribution is also influenced by *transporters,* membrane proteins that facilitate the movement of molecules across the cell membranes. Transport systems are often directional, and they can transport drugs into (influx) or out of (efflux) cells. In either case, the transport system can transfer molecules and create and maintain a concentration difference between two sides of the cell membrane. For example, when some antibiotics diffuse into cancer cells, they are transported out by a multidrug resistance protein (MRP1), which maintains a concentration gradient with

the drug outside the cell. The presence of MRP1 suggests that various drugs that require intracellular access for activity will be ineffective because the transporter removes molecules from inside the cell as quickly as they can diffuse in.

Transport systems also form the basis for distribution into protected tissues. P-glycoprotein, an efflux secretory transporter, is widely distributed and limits the entry of drugs into the brain, testes, intestines, and other sites. Depending on the site, inhibition of P-glycoprotein can result in increased intestinal absorption or distribution into the brain or testes.

Transport systems also affect distribution to sites of metabolism. Transport or diffusion of a drug into cells is required for intracellular metabolism, and transport systems can control how much of a drug is available to an intracellular enzyme for metabolism.

Volume of Distribution

The volume of distribution (V_D) is a hypothetical value that reflects the volume in which a drug would need to be dissolved to explain the relationship between dosage and blood levels (Rice, 2014). If we administer a dose of 100 mg and the plasma concentration is 2 mg/L, then it appears the drug is distributed in 50 L. If we administer the same dose and the plasma concentration is 20 mg/L, then it appears as though the drug is distributed in a volume of 5 L (Fig. 2–9).

V_D is important not only because it relates dosage to blood level but also because it tells us something about where a drug might be distributed. Drugs that are confined to the bloodstream will have a volume of distribution equal to the blood volume. The plasma volume is really the smallest volume of distribution we will encounter because it is not possible for drugs to confine themselves to part of the circulation volume. Plasma makes up approximately 4.5% of body weight, or about 3 L for an average person. Total body water is approximately 50% to 60% of body weight (35–40 L), depending on gender and amount of body fat. Total body water is about two-thirds intracellular and one-third extracellular.

V_D is hypothetical, however, so it may also be higher than the amount of volume. For example, a V_D can represent distribution into an amount of water greater than the total body volume; this suggests that much of the drug is bound somewhere outside the bloodstream.

Metabolism

Metabolism is an important factor in determining drug activity. When drugs are metabolized, they are chemically altered by enzymes into new molecules called *metabolites.* Metabolism can increase or decrease the onset, duration of action, and toxicity of a medication (Rice, 2014). It is important to know how metabolism affects drug activity and pharmacokinetics and how other drugs might interact with a drug to alter its metabolism.

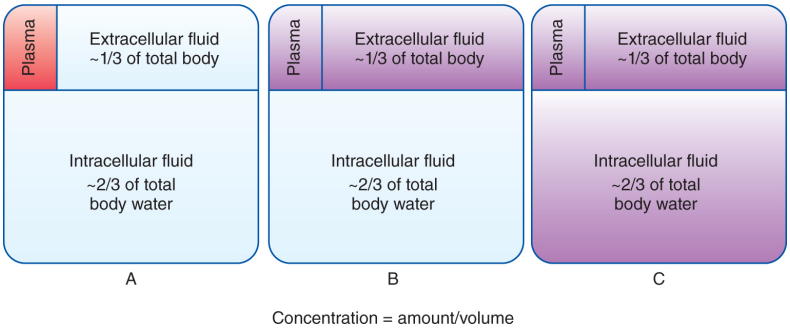

Figure 2–9. Drug concentration in the plasma following administration depends on the volume of distribution. If a drug is confined to plasma (A), then plasma concentration will be higher compared with distribution into extracellular fluid (B) or intracellular fluid (C). Dilution in increasing volumes is shown by shading of the areas containing a drug.

The body is a large container of enzymes that catalyze many chemical reactions required to maintain life. If you think about it, one of the requirements for sustainable life is the ability to maintain a constant internal environment. All organisms are exposed to molecules that cannot be used for food or energy. If an organism cannot rid itself of a certain molecule, then that molecule can accumulate until it causes some sort of toxicity. Therefore, the human body has developed a series of enzymatic reactions directed at all sorts of molecules encountered during life. Drugs that are lipid soluble or weakly acidic or basic may not readily be excreted from the body. In general, the idea is to make these molecules more water soluble so they can be excreted by the kidneys.

Metabolism is the process of changing one chemical into another, and the process usually either creates or uses energy. Metabolism of drugs can

occur in every biological tissue, but it occurs mostly in the smooth endoplasmic reticulum of cells in the liver (Buxton & Benet, 2011). The liver is a major organ for drug metabolism because it contains high amounts of drug-metabolizing enzymes. It is also the first organ encountered by drugs once they are absorbed from the gastrointestinal tract. Metabolism by the liver following oral administration is called *first-pass metabolism* and is important in determining whether a drug can be orally administered.

There is a "family" of enzymes called *cytochrome P450* (CYP; pronounced *sip*) that metabolizes drugs. Each of these CYP enzymes is responsible for a single type of metabolic reaction. A drug may undergo several of these biological transformations, or biotransformations, sometimes in different body tissues, before being excreted. Understanding drug metabolism through these CYPs can provide a framework for understanding metabolism in individual patients as well as drug interactions between medications and with food.

Phase I and Phase II Metabolism

Drug metabolism utilizes two types of reactions that prepare and tag molecules for excretion. Phase I reactions, called *nonsynthetic reactions,* involve oxidation, reduction, and hydrolysis reactions. Phase I reactions introduce or unmask polar groups that, in general, improve water solubility and prepare drug molecules for further metabolic reactions. Phase I metabolism can result in metabolites with greater or lesser pharmacological activity. Many phase I metabolites are rapidly eliminated, whereas others go on to phase II reactions (Fig. 2–10).

Phase II reactions are called *synthetic* or *conjugation reactions* because drug molecules are metabolized and something is added to the drug to synthesize a new compound. Metabolites are linked, or conjugated, to highly polar molecules such as glucuronic acid, glycine, sulfate, or acetate by specific enzymes. Conjugation to these molecules makes metabolites more water soluble and more easily excreted by the kidneys, so the presence or activity of these enzymes can influence the pattern of drug activity and the duration of action for drugs.

Cytochrome P450

The most thoroughly studied drug metabolism reaction is the CYP P450 mixed-function oxidase reaction. This reaction catalyzes the metabolism of a large number of diverse, highly lipid-soluble drugs and chemicals. CYPs

transfer electrons from the oxidation of drugs to the electron transport system of the endoplasmic reticulum, a cell organelle. There are many forms of CYP that are products of separate and distinct genes and that catalyze different reactions. Over 50 human CYPs have been isolated so far. CYPs are organized into numbered families based on their function; for example, the CYP1, CYP2, and CYP3 families metabolize a variety of drugs and steroids (Box 2–5). Subfamilies are designated by additional letters and individual enzymes by numbers. The CYP3As are the major subfamily expressed in the human liver and consist of three forms: CYP3A4, CYP3A5, and CYP3A7. The CYP3A7 enzyme is present in fetuses and appears to be discontinued after birth. CYP3A4 is a major drug-metabolizing enzyme, whereas CYP3A5 metabolizes the same drugs but is less active.

Single nucleotide polymorphisms (SNPs) are minor mutations in proteins that can result in metabolic activity changes. These alterations in DNA are sometimes associated with population groups and help explain why certain patients are more or less sensitive to certain drugs. When SNP variations exist in the individual CYP enzyme, they are named by an asterisk and a number showing the order in which each SNP was identified. For example, there are several CYP2D6 isoforms: CYP2D6*1 (with no mutation), CYP2D6*3, CYP2D6*4, and up to CYP2D6*17. Metabolic activity for each isoform may be decreased, normal, or increased. We inherit our drug-metabolizing enzymes, so it is possible to have two isoforms that differ in expression and activity. About 7% of the U.S. population lacks CYP2D6 enzyme activity. Other patients exhibit a range of enzyme activities, with some ethnic groups having a significant percentage of ultrafast metabolizers. As you can imagine, there is the potential for a good deal of metabolic variability among individual patients.

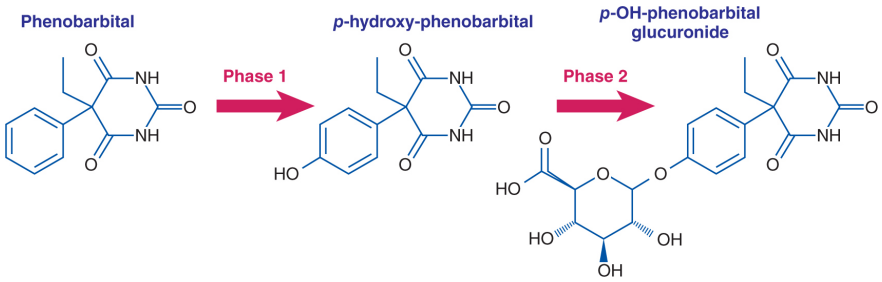

Figure 2–10. Metabolism of phenobarbital. Phase I metabolism adds an –OH to the molecule. A water-soluble glucuronide molecule is linked to this site during phase II metabolism.

BOX 2–5 DRUG-METABOLIZING ENZYMES (LISTED IN ORDER OF IMPORTANCE)

- CYP3A
- CYP2C
- CYP1A
- CYP2E
- CYP2D

CYP3A4 is a prominent enzyme responsible for metabolism of a number of drugs and serves as a good example of a CYP enzyme. Drugs that are metabolized by CYP3A4 include azole antifungals; some statin drugs that inhibit HMG-CoA (5-hydroxy-3-methylglutaryl-coenzyme A) reductase and lower cholesterol; the corticosteroids prednisone, prednisolone, and dexamethasone; the anticonvulsant carbamazepine; and many other drugs. Note the variety of drug classes and chemical structures that are metabolized by this enzyme.

Variations in CYPs and their activity can result in marked differences in drug metabolism between individuals. Individual variation in drug metabolism contributes to drug–drug and some drug–food interactions. Enzyme induction occurs when drug treatment results in an increase in enzyme activity, usually limited to the enzymes responsible for metabolizing the drug. Enzyme induction results in an increase in metabolism that decreases the amount of drug and increases the amount of metabolite in the body.

Competition occurs when two drugs are metabolized by the same enzyme. Often the enzyme can metabolize both drugs, but sometimes one drug will be preferentially metabolized, delaying the metabolism and extending the half-life of the competing drug.

Metabolism and Half-Life

The rate of drug metabolism depends on the blood levels of drug in relation to the affinity of the drug for its metabolism enzymes. Most drugs are present at concentrations below their K_m for metabolism (the concentration at which metabolism is half of maximum). Under these conditions, metabolism is related to drug concentration so that a fixed *fraction* of drug is metabolized per hour. This is called *first-order metabolism* and is characterized by a half-life, the time period over which the drug concentration will decrease by half. Therefore, blood levels decrease by 50% in one half-life, 75% in two half-lives, and 87.5% in three half-lives. As a general rule, drugs tend to be administered at dosing intervals that are close to their half-life.

Some drugs—ethanol is the prototype—are present at concentrations well above their K_m for metabolism. When this happens, enzymes act near to their maximal metabolic capacity and metabolize a constant *amount* of drug each hour. This is called *zero-order metabolism.*

Rarely, but importantly, some drugs are present at blood concentrations that range from below to above the K_m for their metabolism. At lower doses or concentrations, they are metabolized like typical drugs, but at higher doses or concentrations their metabolism is limited. Phenytoin is a prototypical example of a drug with "mixed-order," or Michaelis–Menten, pharmacokinetics. Above a certain level of phenytoin dosing (about 300 mg/day in adults), dosage must be adjusted by small amounts, which can produce disproportionate increases in blood levels as metabolism changes from first order to zero order.

Patterns of Metabolism

It is important to remember that metabolism can change the pharmacological activity of drugs. We typically consider that drugs are pharmacologically active and that metabolism decreases the activity and promotes excretion (Fig. 2–11), so we expect to see inactive metabolites

that have short half-lives and are rapidly excreted. This is not always the case, however.

Prodrugs are inactive compounds that rely on metabolism to become active. Prodrugs have advantages and disadvantages. The advantages may be in terms of their absorption or distribution. L-DOPA is a prodrug used to treat Parkinson disease. The problem in Parkinson disease is a lack of dopamine in the striatum of the brain. Dopamine, however, cannot pass through the blood–brain barrier, so it is ineffective when used to treat the neurotransmitter shortage in the brain. L-DOPA can pass into the brain and enter into cells, where it can be converted into dopamine.

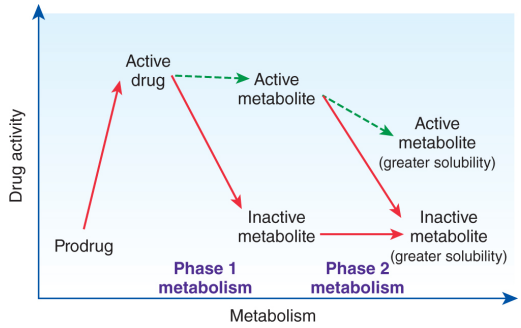

Figure 2–11. Typical effect of metabolism *(solid arrows)* on drug activity. Prodrugs are metabolized to active drugs that can undergo phase I and phase II metabolism, with metabolites varying in activity compared with the parent drug, and in solubility, which increases the likelihood of renal elimination. Sometimes metabolism produces unusual effects *(dashed arrows),* such as drug metabolites that retain drug activity or accumulate in the body.

Prodrugs can also have disadvantages. Terfenadine was one of the first nonsedating antihistamines and was popular at one time. First-pass metabolism by CYP3A4 biotransforms terfenadine, which is cardiotoxic, into fexofenadine, an effective antihistamine. When it was realized that inhibition of CYP3A4 could result in toxicity and death in some patients, terfenadine was withdrawn and replaced with fexofenadine, its active metabolite.

Other prodrugs are pharmacologically inactive and rely on biotransformation to an active metabolite. CYP2D6 metabolizes codeine into morphine, which is a 12 times more potent opioid. Hydrocodone is

metabolized to the more potent opioid hydromorphone by CYP2D6 as well. About 7% of the White population lacks CYP2D6 activity. Administration of a prodrug requiring metabolism by CYP2D6 creates a situation in which the patient is receiving an inactive or poorly active drug. In the case of pain relievers, patients may be seeking stronger drugs not because of abuse but because the drugs are not being biotransformed into their active metabolites. In contrast, patients with highly active CYP2D6 are at greater risk for opioid toxicity following administration of codeine or hydrocodone. As in Figure 2–8, rapid conversion results in higher blood levels and increased risk of adverse effects.

Meperidine is an opioid analgesic that is used parenterally and orally to treat pain and postoperative shivering. It is metabolized by CYP2B6, 2C19, and 3A4. Meperidine remains present in the body a relatively short period of time; its half-life is 3 to 4 hours. Meperidine's metabolite, normeperidine, is more toxic and remains in the body for a much longer period of time; its half-life is 14 to 21 hours in patients with typical renal function and even longer in those with poor renal function. This difference in half-lives creates a clinical situation in which meperidine is administered frequently and levels of normeperidine will rise until toxicity presents as irritability, tremors, delirium, and seizures in patients with poor renal function. The solution is to avoid meperidine use in at-risk patients and limit administration of meperidine so that normeperidine does not accumulate.

Drug Interactions

Alterations in biotransformation are responsible for many drug–drug and drug–food interactions. There are a limited number of drug-metabolizing enzymes, and these enzymes can metabolize only one drug molecule at a time. Compounds compete for enzymes based on their chemical affinity; chemicals with higher affinity for a particular CYP or drug-metabolizing enzyme will be preferentially metabolized. Thus, a drug that can be metabolized by multiple enzymes will be biotransformed by each enzyme in proportion to the affinity. When several drugs are metabolized by a single enzyme, each drug will be metabolized in proportion to the affinity for each of the drug–enzyme interactions. If one drug monopolizes the enzyme, then it can block the biotransformation of other drugs, extending their time in the

body and contributing to toxicity. Thus, when we look for drug interactions, we often look for drugs that are metabolized by the same CYPs.

CYP3A4 is particularly problematic because it metabolizes so many different drugs. Consequently, there is a greater likelihood of interference with metabolism when a patient receives a number of drugs. In addition to other sites in the body, such as the liver, CYP3A4 activity is present in the cells lining the gastrointestinal tract and can be influenced by food as well as drugs. Grapefruit juice contains a substance that inhibits CYP3A4 and can sometimes markedly increase blood levels of drug in patients consuming grapefruit juice. Surprisingly, this interaction extends to patients consuming grapefruit juice within about a day before drug administration. This interaction can affect a number of drugs, such as several older statin drugs that have increased blood levels in the presence of grapefruit juice. Higher blood levels are not always bad, but it is appropriate to counsel patients to avoid potential toxicity resulting from CYP3A4 interactions and inhibition.

Some drugs increase the expression of drug-metabolizing enzymes, which is called *enzyme induction.* Induction can be due to either increased enzyme synthesis or decreased enzyme degradation. Pharmacotherapy with phenobarbital, for example, effectively induces CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, and CYP3A4. Induction increases the biotransformation of drugs and can encourage variations in metabolism and generally increase the removal of drugs by metabolism.

In clinical practice, transport systems and metabolic enzymes work together in the biotransformation of drugs. Drugs are transported into cells where they can be metabolized. Patients can have genetic differences in their ability to transport drugs through cell membranes, leading to additional variation in metabolism and drug response.

We generally assume that metabolism of drugs results in a product that has less pharmacological activity and is more likely to leave the body. Metabolism, or biotransformation, can actually result in either an inactive or an active metabolite. Metabolites are generally excreted more rapidly, but sometimes metabolite excretion is delayed. Drugs may interact with more than one CYP enzyme to produce multiple metabolites with different levels of activity and excretion.

Excretion

Excretion is the process in which drugs are transferred from inside the body to outside the body. Just as drugs pass a biological boundary from outside to inside for absorption, so they must pass in the opposite direction, although not necessarily in the same location, for elimination.

The locations at which drugs can pass from inside the body to outside include some sites that are familiar as sites of absorption, such as lungs, skin, and intestines. There are also some unique sites where drugs are excreted but not absorbed. These include the kidney and the gallbladder. The principal organs for drug elimination are considered to be the kidneys, lungs, biliary system, and intestines. Any individual drug may rely on one or more of these sites for elimination or on a different site, such as skin excretion or excretion into saliva or breast milk.

Renal Excretion

The kidney is the primary organ of excretion for most drugs. The general mechanism of metabolism is to produce drug metabolites that are more water soluble and thus easier for the kidneys to remove from the plasma and excrete in the urine.

The kidney is a complex organ with several important functions, including excretion of waste products and maintenance of fluid and electrolyte balance in the body. Its strategy is to allow removal of a large volume of plasma and then to take back the substances that the body needs. The resulting waste product is urine. There are also transport mechanisms that can secrete substances into the urine. We will consider how drugs end up in the urine.

Production of urine begins in the glomerulus of the kidney. The operational unit of the kidney is the nephron, and each of the approximately 1 million nephrons begin with a glomerulus (Fig. 2–12). The glomerulus is a specialized area of the nephron adapted for ultrafiltration, a process in which substances in the plasma pass through small holes, or pores, in the glomerular capillary membrane based on their size and charge. The structure of the glomerular capillary membrane permits filtration of smaller molecules while restricting the passage of compounds with larger molecular weights. As blood flows through the kidney and encounters the glomerulus, much of the fluid portion of the blood is filtered into the lumen, or center, of the nephron. The kidney is exceptionally efficient at what it does. Approximately 125 mL of blood flows through the glomeruli in the kidneys

per minute, called the *glomerular filtration rate* (GFR), which is an important measure of renal function.

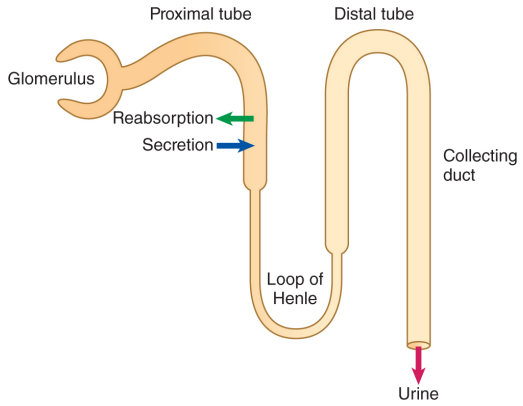

Figure 2–12. Diagram of the nephron, the functional unit of the kidney. Blood vessels flowing into the glomerulus provide blood, which is filtered into the lumen, the inner opening of the nephron. As fluid passes along the nephron, transporters can either reabsorb drugs *(green arrow)* back into the blood or secrete *(blue arrow)* drugs from blood into the lumen.

Glomerular filtration is the first step toward production of urine containing excreted drug. Filtration preserves plasma proteins while removing free drugs and other waste products from the plasma. The large volume of fluid filtered through the glomerulus is an ideal vehicle for drug removal. As the ultrafiltrate is formed, drugs that are free in the plasma and not bound to plasma proteins or blood cells are filtered. Filtration may be slower for large-molecule drugs because of the size of the pores through which filtration occurs; very large drugs may not be filtered at all. The pores of the glomerulus contain a fixed negative charge, so filtration may also be affected by drug charge.

The glomerular filtrate in the nephron contains a variety of smaller molecules, including excreted drug and metabolites. As the filtrate moves through the lumen of the nephron, molecules are reabsorbed from the lumen into the blood. The extent to which a drug diffuses back across the nephron to reenter the circulation is one of the factors that determine urinary excretion of drug. The passive diffusion of substances back into the circulation is encouraged by the reabsorption of water that occurs along most of the nephron. This creates a concentration gradient promoting

reabsorption if the lipid solubility and ionization of the drug are appropriate.

The un-ionized or uncharged form of the drug will diffuse more readily, and the acidity of urine can influence the ionization and reabsorption of drugs. Acidification of the urine creates an “ion-trapping” situation that favors the excretion of basic drugs and metabolites, whereas basic urine encourages the excretion of acidic drugs and metabolites. Effects of urine acidity on drug elimination can have important clinical implications, particularly when manipulated clinically to enhance the elimination of toxic drugs. Urine can be made acidic by administration of ammonium chloride or can be made basic by administration of sodium bicarbonate.

Tubular Reabsorption

In addition to reabsorption by passive diffusion, some substances filtered at the glomerulus are reabsorbed by active transport systems located primarily in the proximal tubule of the nephron. Active transport is important for endogenous substances that the body needs to recover from the glomerular filtrate, such as ions, amino acids, and glucose. The active transport systems are located on the luminal cell surface and transport substances into the cell, where they are passively transported into the plasma.

A small number of substances may be actively reabsorbed. It is more common that drugs acting on tubular secretion do so by inhibiting active transport. Uricosuric agents such as probenecid and sulfinpyrazone inhibit the active reabsorption of uric acid. Sodium-glucose cotransporter 2 (SGLT2) inhibitors, such as canagliflozin, are newer diabetes medications that reduce the reabsorption of glucose, resulting in loss of glucose in the urine. Substances that are actively reabsorbed can also be actively secreted, and drugs may inhibit both processes. For example, low doses of salicylates, such as aspirin, inhibit tubular secretion and decrease total urate excretion, whereas higher doses inhibit tubular reabsorption and result in increased excretion of uric acid.

Tubular Secretion

The nephron also contains active secretory systems that transport drugs from the blood into the lumen of the nephron. There is a transport system that secretes organic anions and one that secretes organic cations. The transporters are present on the plasma side of the tubular cells of the nephron, where they actively pump anions or cations into the cell. The

substances then pass into the lumen by passive or facilitated transport. The secretory capacity of these transporters can be saturated so that less drug is excreted at high drug concentrations. When two drugs are substrates for the same transporter, they compete with one another and decrease the rate at which each is excreted.

Active secretory systems for anions and cations are important because anions and cations are often strongly bound to plasma proteins and may not be readily excreted by glomerular filtration. Tubular secretion often contributes to the renal elimination of drugs that have short half-lives. Hydrochlorothiazide, furosemide, penicillin G, and salicylates are among the substrates for the organic anion transport system. The organic cation transport system actively secretes atropine, cimetidine, morphine, and quinine.

Renal Excretion of Drugs

The rate at which a drug is excreted by the kidneys depends on several factors. Renal blood flow influences the GFR. Filtration in the glomerulus depends on the molecular size, the charge, and the degree of protein binding, each of which influences how much drug passes through the glomerular basement membrane. Tubular acidity will influence the degree of reabsorption. Active reabsorption or active secretion into the urine may also influence excretion rate.

Renal excretion of drugs is typically well characterized. What is variable, however, is the level of renal function in an individual patient. It is common to monitor renal function of patients in the clinical setting and adjust dosages based on renal function and the renal contribution to overall drug excretion. Renal function is typically assessed from patient serum creatinine along with height, weight, age, and gender.

Biliary Excretion

In addition to metabolizing many drugs, the liver secretes about a liter of bile each day. Drugs can enter the bile and be excreted into the intestinal tract when bile is released to help digest food. Only small amounts of drug enter the bile by diffusion; instead, biliary excretion contributes to removal of some drugs. The biliary system includes three types of active transport. Organic cation and organic anion transporters are similar to those found in the renal tubules. The additional system is the bile acid transport system. Conjugated metabolites of drugs generally have enhanced biliary excretion.

Cardiac glycosides, such as digoxin, are an example of drugs secreted into the bile.

Some drugs that are excreted in bile can be reabsorbed in the intestine. This creates a phenomenon called *enterohepatic cycling,* in which drug is excreted in the bile, absorbed from the intestines, and then excreted in the bile again. Enterohepatic cycling decreases the amount of drug that is actually excreted and extends the time that a drug remains in the body.

Other Sites of Excretion

Drug excretion is not limited to the kidneys and liver. Drugs can diffuse out of the body at various sites, and although these excretion sites are typically not major, they can be important for forensic or clinical reasons.

Pulmonary excretion can occur for any volatile material present in the body. Pulmonary excretion is important for anesthetic gases, such as nitrous oxide, and after alcohol consumption. Ethanol distributes throughout body water and is readily excreted each time we breathe. Because the amount of ethanol exhaled in each breath is proportional to blood level, the Breathalyzer(tm) can be used to estimate blood levels of ethanol. Pulmonary excretion is also important for volatile ketones, which are produced in patients whose diabetes is poorly controlled. The smell of ketones on a patient's breath can be an important clue that the patient may have diabetes and be at risk for diabetic ketoacidosis.

Substances can be excreted through the skin, although this is often a minor route of elimination. The skin has a large surface area through which excretion can occur; drugs may be incorporated into the hair and can be excreted through the sweat glands. Excretion of drugs into sweat and saliva is of minor importance for most drugs and depends on the diffusion of uncharged drug across the epithelial cells of sweat and salivary glands. Excretion into hair, sweat, and saliva is quantitatively unimportant but can be used to noninvasively detect drugs in the body. Interestingly, some drugs excreted into saliva can produce changes in taste. Excretion into saliva might help explain part of the pharmacological action of certain drugs, such as the antibiotic erythromycin, when used for throat infections.

Drugs can also be excreted into the breast milk of nursing mothers. The concentration in the breast milk depends on drug properties such as lipid solubility and the degree of ionization. It can also depend on an individual patient's particulars, such as the extent of active secretion into breast milk

and the blood level of the drug in the mother. Low molecular weight drugs that are un-ionized can passively diffuse across the epithelial cells of the mammary gland and enter the breast milk. Because breast milk is more acidic than plasma, it tends to accumulate basic drugs.

Infants can be exposed to drugs through breast milk. The risk to the infant from drug exposure in breast milk depends on the amount and type of drug involved and the ability of the infant to metabolize the drug. Breastfeeding is discouraged when there is a potential for drug toxicity in the infant.

SUMMARY

The rational use of drugs is based on a foundation of chemical and physiological principles. Drugs interact with specific sites, called *receptors,* according to chemical laws. Higher concentrations of drug produce more interactions and greater effects. How rapidly a drug is absorbed, distributed, metabolized, and excreted dictate local concentrations of a drug that produce clinical effects. The onset and duration of a drug effect reflect the pharmacokinetics of the drug and the properties of the receptor. Sound therapeutic decisions draw on the unifying foundational principles of pharmacology.

REFERENCES

Buxton, I. L. O., & Benet, L. Z. (2011). Pharmacokinetics: The dynamics of drug absorption, distribution, metabolism and elimination. In Burton, L. L., Chabner, B. A., & Knollmann, B. C. *Goodman & Gilman: The pharmacological basis of therapeutics* (12th ed.). New York, NY: McGraw-Hill.

Kenakin, T. P. (2005, October). New bull's-eyes for drugs. *Scientific American, 293*(4), 50–57.

Rice, P. J. (2014). *Understanding drug action: An introduction to pharmacology*. Washington, DC: American Pharmacists Association.

CHAPTER 3

RATIONAL DRUG SELECTION

Teri Moser Woo

The process of prescribing medication requires a thoughtful, evidence-based approach to drug selection. The World Health Organization (WHO)