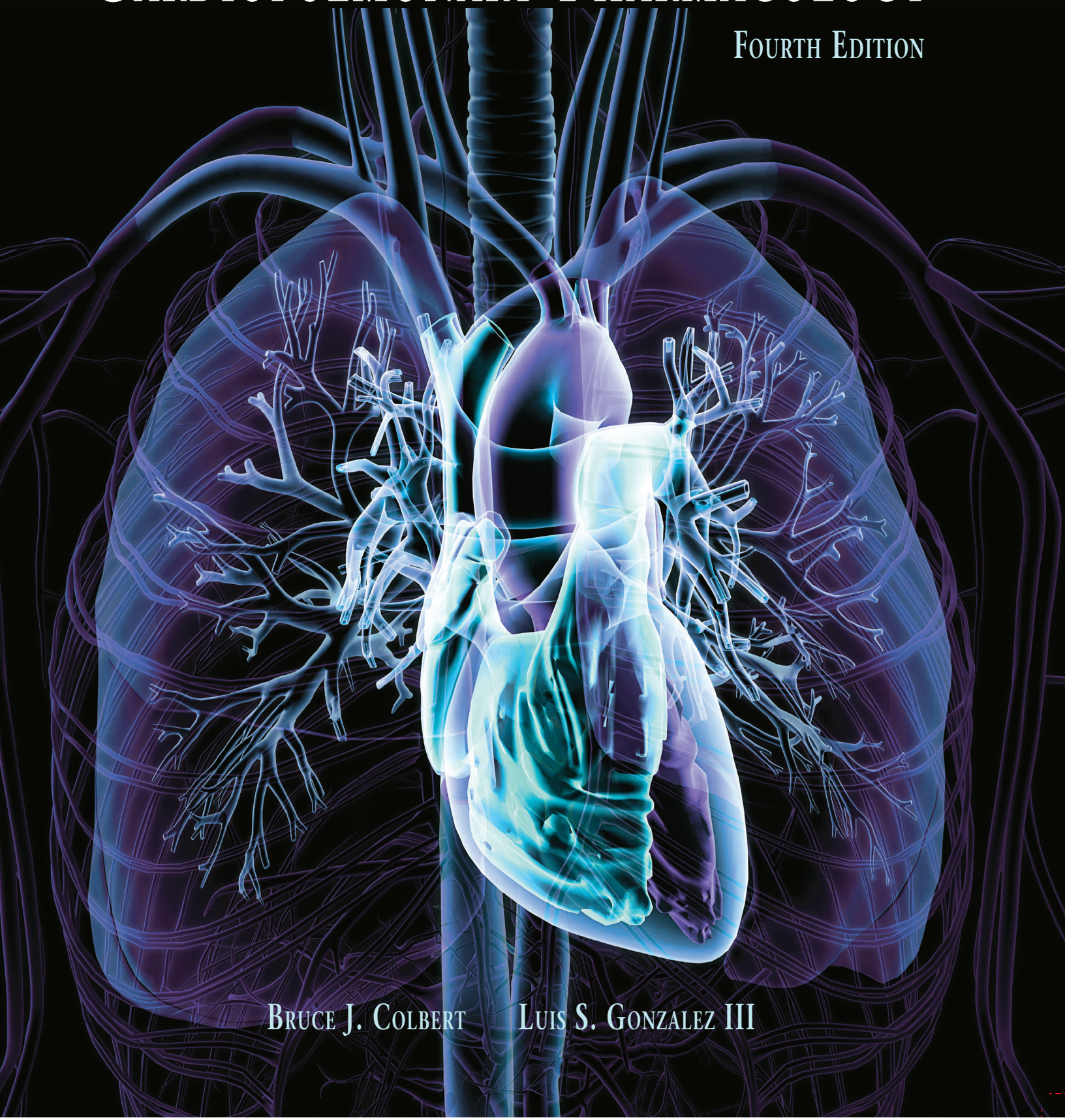
Integrated Cardiopulmonary Pharmacology

Fourth Edition



Bruce J. Colbert Luis S. Gonzalez III


INTEGRATED CARDIOPULMONARY PHARMACOLOGY

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BRUCE J. COLBERT, MS, RRT
Director of Allied Health
Associate Professor
University of Pittsburgh at Johnstown

LUIS S. GONZALEZ III, PharmD, BCPS
Director, Pharmacy Practice Residency Program
Manager, Clinical Pharmacy Services
Conemaugh Memorial Medical Center
Johnstown, PA

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Dedications

In memory of my parents, Robert and Josephine Colbert, who taught me the importance of family and education, and to my loving wife, Patty, and two great children, Joshua and Jeremy, who continue to teach me its importance.

—Bruce J. Colbert

In memory of my father, Luis Gonzalez Jr., who taught me the value of hard work, and to my mother, my wife Stephanie, Stephen, Christopher, and Luke for their love and support.

—Luis Gonzalez III

About the Authors

Bruce Colbert is Clinical Associate Professor and Director of the Allied Health Department of the University of Pittsburgh at Johnstown. He has authored ten books, developed an interactive worktext and DVD program on student success, and given over 300 invited lectures and workshops at both the regional and national level. Many of his workshops are with educational programs on improving teaching effectiveness by utilizing active teaching and learning techniques to make the medical sciences relevant to today's students. Bruce is most proud of his volunteer work with wounded veterans, helping them to successfully transition into the workplace.

Dr. Luis S. Gonzalez III is an Associate Program Director in the Department of Internal Medicine Residency Program at Conemaugh Memorial Medical Center, where he also serves as the Clinical Coordinator for Pharmacy Services and directs a Pharmacy Residency Program. He is a Clinical Associate Professor for the Schools of Pharmacy at the University of Pittsburgh, Duquesne University, and Ohio Northern University. He has authored numerous peer-reviewed publications and has presented at regional and national conferences. Dr. Gonzalez was one of the original founders of the Johnstown Free Medical Clinic.

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PART 3: PUTTING IT ALL TOGETHER

Foreword

Pharmacology is often perceived as one of the more difficult subjects in a medical curriculum. There are several possible explanations for this. First there are the difficult concepts and terms that are inherent to this subject. Second there is the massive amount of information that must be covered, which is often presented in a dry and highly technical manner. Finally this is a constantly evolving field of new breakthroughs, drugs, and delivery devices. We took all of these factors into account as we developed and pilot-tested this innovative project. So what makes this book unique and able to address these concerns?

First and foremost this truly is an *integrated* project—this is not just a buzzword thrown into the title. The authors and publisher took very seriously the integrated aspect of this project and sought the interdisciplinary perspective offered by both pharmacists and respiratory therapists. The end result is a book that fully integrates both anatomy and physiology concepts and pathophysiology concepts in relationship to pharmacology and heavily integrates clinical practice and application in all the related therapeutic drug classifications. Moreover, it is integrated in the way the book is set up. Part One covers overall pharmacological principles, dosage calculations, the autonomic nervous system, and medication aerosol therapy to lay the groundwork for the specific drug categories found in Part Two (bronchodilators, mucokinetics, surfactants, anti-inflammatory, anti-asthmatics, anti-infective, cardiac, neuromuscular, and therapeutic gases). Part Three then integrates and "puts it all together" to show the integrated approach to the management of COPD, asthma, infectious respiratory disease, and advanced cardiac life support. All of this integrated material was then incorporated into the text in a style that does not distance the student from the material; the authors took very seriously the concept of writing and strove to encourage learning and relating the material, rather than massive memorization.

Finally there are some things we did not take so seriously. While we were serious about the contents, relevancy, and accuracy of the material, we also had fun writing, researching, and collaborating on this project. We utilized splashes of humor in this textbook, with the underlying idea that what is learned with humor is not readily forgotten. In addition we used a conversational writing style, rich with analogies, to make the learning experience comfortable and relatable. In other words we wrote it for the students and not to impress our colleagues.

Acknowledgments

The fourth edition of this text has an interesting backstory. After publishing the first three editions, Pearson Publications discontinued their line of respiratory textbooks. As authors, we were gratified by the success of the first three editions and were eager to find a new publisher for the fourth edition. We were very fortunate to find BVT Publishing, whose philosophy of publishing high-quality yet affordable textbooks geared toward the students matched our own.

Pearson deserves a great deal of credit and thanks for their professional help in making this transition a smooth one. We would also like to thank the BVT Publishing team, including Nate Shankles and Richard Schofield, for their professionalism and enthusiastic support of this textbook; our copy editor Anne Schofield; and Shannon Conley and her production team, who helped pull everything together to create this fourth edition. The authors also wish to thank Esther Scannell for her creative design work and Tara Joffe for her thorough proofreading. Bruce Colbert wants to personally thank the University of Pittsburgh at Johnstown's Respiratory Care classes, which continue to give input into the concept of this project and keep the vision student friendly.

Preface

New to This Edition

Working with BVT has given us the exciting challenge of redesigning the book to make it even more user friendly. We were also able to enhance the text with BVTLab®, which further supports instructors and students alike. All materials have been updated with a special focus on the latest available approved drugs in all therapeutic classifications. These updates include the following:

- Updated asthma and COPD information with the latest assessment and treatment guidelines
- Updated therapeutic drug categories
- New tables that concisely present drug categories, dosages, and special considerations
- A new book design and new illustrations and photos enhancing presentation and facilitating visual learning

But it is also very important to note what we did not change: We strove to maintain the same user-friendly writing style that has been well received in the first three editions and to keep the rich use of analogies that has helped students to truly learn the material—rather than requiring them to rely on massive short-term memorization.

Pedagogical Features

Our goal is to continue to produce a truly introductory and interactive pharmacology text that students can connect with and use to learn pharmacology. Several features have been incorporated into the textbook to help accomplish that goal; they include the following:

Learning Hints and Controversies

These special features in each chapter ensure understanding of difficult concepts and stimulate further thought.

Clinical Pearls

Clinical pearls are also interspersed throughout the chapters to connect the knowledge and show the relevancy of learning the material. In addition numerous clinical applications are presented to provide a real-world connection.

Patient and Family Education

Each chapter has a special box that discusses important education issues for both the patient and family.

Life Span Considerations

These boxes discuss issues that may affect the pediatric and geriatric populations pertaining to the concept or drug category being reviewed.

Key Terms

Key terms are boldfaced and included in the glossary. Symbols, units, and abbreviations of medical terms are defined in the chapter opener for easy reference.

Review Questions

Periodic "Time for Review" problems within each chapter help to ensure concept understanding before a student moves on to the next topic. Comprehensive questions—which build from multiple-choice and matching questions to higher-level critical thinking and case-study questions—are also included at the end of the chapter.

BVT*LAB*®

BVT*Lab* provides two areas of support for instructors and students. The Student Study Center includes resources such as eBooks, study guides, practice quizzes, flashcards, chapter summaries, multimedia content and so on, and the Online Classroom incorporates grade book, discussion forums and delivery of online assignments, quizzes, and exams.

Supplements and Resources

Instructor's Supplements

A complete teaching package is available for instructors who adopt this book. This package includes an online lab, instructor's manual, test bank, course management software, and PowerPoint® slides.

BVT*Lab*	An online lab is available for this textbook at www.BVTLab.com, as described in the BVT*Lab* section below.
Instructor's Manual	The instructor's manual helps first-time instructors develop the course and offers seasoned instructors a new perspective on the material. Each section of the instructor's manual coincides with a chapter in the textbook. The user-friendly format starts with chapter summaries, learning objectives, key terms, and detailed outlines for each chapter. Then the manual presents sample answers to chapter review questions and case studies, lecture suggestions, and classroom activities. Lastly, additional resources—books, articles, websites—are listed to help instructors review the materials covered in each chapter.
Test Bank	An extensive test bank is available to instructors in both hard copy and electronic formats. Each chapter has 50 multiple choice, 25 true or false, 10 short answer, and 5 essay questions. Each question is ranked by difficulty and style and referenced to the appropriate section of the text to make test creation quick and easy.
Course Management Software	BVT's course management software, Respondus, allows for the creation of tests and quizzes that can be downloaded directly into a wide variety of course management environments such as Blackboard, WebCT, Desire2Learn, ANGEL, E-Learning, eCollege, Canvas, Moodle, and others.
PowerPoint Slides	A set of PowerPoint® slides is available for each chapter and contains slides for the chapter overview, learning objectives, chapter outline, key topics, and summary and conclusion.

Student Resources

Student resources are available for this textbook at www.BVTLab.com. These resources are geared toward students needing additional assistance, as well as those seeking complete mastery of the content. The following resources are available:

Practice Questions	Students can work through hundreds of practice questions online. Questions are multiple choice, true/false, or short answer in format and are graded instantly for immediate feedback.
Flashcards	BVT*Lab* includes sets of flashcards that reinforce the key terms and concepts from each chapter.
Chapter Summaries	A convenient and concise chapter summary is available as a study aid.
PowerPoint Slides	All instructor PowerPoints are available for convenient lecture preparation and for students to view online for a study recap.

BVT*LAB*

BVT*Lab* is an affordable online lab for instructors and their students. It includes an online classroom with a grade book and chat room, a homework grading system, extensive test banks for quizzes and exams, and a host of student study resources as described below.

Course Setup	BVT*Lab* has an easy-to-use, intuitive interface that allows instructors to quickly set up their courses and grade books, and to replicate them from section to section and semester to semester.
Grade Book	Using an assigned passcode, students register for the grade book, which automatically grades and records all homework, quizzes, and tests.
Chat Room	Instructors can post discussion threads to a class forum and then monitor and moderate student replies.
Student Resources	All student resources for this textbook are available in BVT*Lab* in digital form.
eBook	Students who have purchased a product that includes an eBook can download the eBook from a link in the lab. A web-based eBook is also available within the lab for easy reference during online classes, homework, and study sessions.

CUSTOMIZATION

BVT's Custom Publishing Division can help you modify this book's content to satisfy your specific instructional needs. The following are examples of customization:

- Rearrangement of chapters to follow the order of your syllabus
- Deletion of chapters not covered in your course
- Addition of paragraphs, sections, or chapters you or your colleagues have written for this course
- Editing of the existing content, down to the word level
- Customization of the accompanying student resources and online lab
- Addition of handouts, lecture notes, syllabus, etc.
- Incorporation of student worksheets into the textbook

All of these customizations will be professionally typeset to produce a seamless textbook of the highest quality, with an updated table of contents and index to reflect the customized content.

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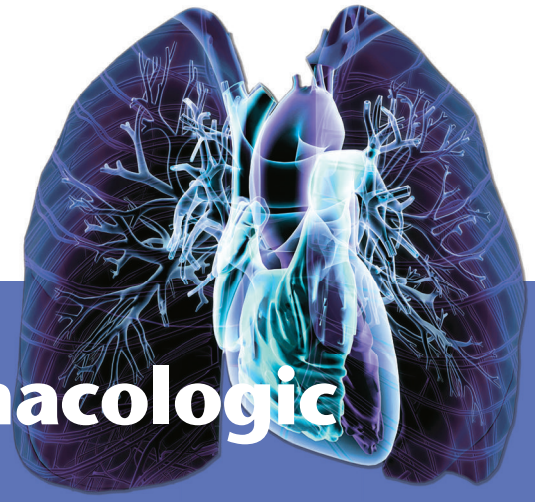
University of Hawaii
Honolulu, Hawai

PART 1

The Basics

Chapter 1



General Pharmacologic Principles

OBJECTIVES

Upon completion of this chapter you will be able to

- Define key terms related to pharmacologic principles.
- Utilize drug reference sources of information.
- Discuss advantages and disadvantages of different routes of administration.
- Describe the processes of drug absorption, distribution, metabolism, and elimination.
- Explain differences in pharmacokinetics, pharmacodynamics, and adverse effects of drugs in pediatric, geriatric, pregnant, and breastfeeding patients.
- Discuss factors that may alter a patient's response to a drug.
- Discuss principles of drug poisonings, adverse drug reactions, and interactions.
- Discuss responsibilities in drug administration.
- Relate the importance of pharmacogenomics to future drug therapy.

KEY TERMS

additive
adverse drug reaction
agonist
antagonist
bioavailability
dependence
desensitization
disease management
efficacy
emetics
enteral route
first-pass effect
formulary
half-life
loading dose
maintenance dose
parenteral route
pharmacodynamics
pharmacogenomics
pharmacokinetics
pharmacology
pharmacotherapy
potentiation
protein binding
racemic
receptor
selectivity
steady state
sublingual
synergism
teratogenic
therapeutic range
therapeutics
tolerance
toxicology
transdermal

ABBREVIATIONS

ACE	angiotensin-converting enzyme
ADR	adverse drug reaction
AHFS	*American Hospital Formulary Service*
CNS	central nervous system
COPD	chronic obstructive pulmonary disease
CPOE	computerized physician order entry
DNA	deoxyribonucleic acid
DPI	dry-powder inhaler
FDA	Food and Drug Administration
GI	gastrointestinal
HIV	human immunodeficiency virus
IM	intramuscular
IV	intravenous
JCAHO	Joint Commission on Accreditation of Healthcare Organizations
MDI	metered-dose inhaler
NG	nasogastric
NIH	National Institutes of Health
NPO	nothing by mouth
OTC	over the counter
PDR	*Physicians' Desk Reference*
PEG	percutaneous endoscopic gastrostomy
PO	by mouth (Latin *per os*)
PR	by rectum
SC	subcutaneous
SL	sublingual
SVN	small-volume nebulizer
$T_{½}$	half-life
USAN	United States Adopted Name Council
USP	United States Pharmacopeia
VD	volume of distribution

For the health-care professional, medication administration carries with it many responsibilities. With the vast array of drugs currently used in the practice of medicine, and new ones constantly being tested and developed, it is an impossible task to know every detail about every drug. However, if one is well-grounded in basic pharmacologic principles, one will know where to look and be able to understand the medical language that describes drugs and their interactions within the human organism.

This chapter discusses fundamental principles of pharmacology and strives to provide you with a healthy respect for drugs and knowledge that you can apply daily in pharmacotherapy decision making. After reading this chapter, you will understand the language of pharmacology and the important concepts for safe and effective drug administration.

1.1 BASIC TERMS

Drugs are among the most important aspects of clinical medicine. **Pharmacology**, the study of drugs and their action on the body, is a discipline that hinges on basic and clinical science. Pharmacology has a very long history. Ancient civilizations used plants containing ephedrine to treat breathing disorders, Native Americans used wild mint to treat stomach disorders—the list could go on. There has also been a darker side, when drugs were manufactured for nonmedical reasons. Examples include the infamous opium dens of the past and, in modern times, dangerous designer drugs that have killed many people.

Whereas pharmacology is a broad term that describes the study of drugs in general, **therapeutics** is defined as the study of drugs used to cure, treat, or prevent disease. Often the terms *pharmacology* and *therapeutics* are combined into the term **pharmacotherapy**. Another recent term that relates to these concepts is **disease management**. Disease management refers to the collective management of all aspects of the patient's disease, not just the use of pharmacotherapy. Pharmacotherapy, however, is usually one of the main components of disease management.

Drugs with similar characteristics are grouped together as a pharmacologic classification or class. One can predict how drugs in a class will act. For example drugs in the xanthine class can stimulate the central nervous system (CNS) and have a diuretic effect (i.e., they increase urine output), among other things. Caffeine, found in coffee, and the prescribed drug theophylline are both in this class and have similar effects, which you are probably aware of if you have ever drank large amounts of coffee. Caffeine usually produces diuresis with doses greater than 250 milligrams/day (mg/day). This text focuses on understanding pharmacologic classes and avoids emphasizing massive memorization of the characteristics of individual drugs. This is important because new drugs are approved every day, and the need for knowledge of pharmacology and therapeutics grows constantly.

Drugs can also be classified by their therapeutic category, such as bronchodilators. A therapeutic category can have several different pharmacological classes, and Chapters 5 through 11 are organized by therapeutic categories. For example, the class of xanthines will be discussed in the chapter on bronchodilators, along with other classes of drugs (beta-adrenergics and anticholinergics) that are also used as bronchodilators.

1.2 DRUG DEVELOPMENT

Drugs are derived from a variety of sources, including plants, animals, minerals, chemicals, and recombinant deoxyribonucleic acid (DNA). Chemicals can be made into drugs synthetically or can be genetically bioengineered. Most drugs today are synthetic, but it is predicted that in the future many will be bioengineered.

The Food and Drug Administration (FDA) is the federal agency that regulates drug testing and approves new drugs for the market. Much to the discontent of animal activists, drugs are first tested on animals. Then each drug must pass three phases of human testing prior to approval. The phases proceed through testing in healthy volunteers (frequently "starving" students of the health-care professions), to testing in people with the disease against which the drug is expected to work, and then to large multicenter trials across the country. Phase IV studies, also called postmarketing studies, are studies performed after the drug is already on the market. They are becoming more frequent and are used to look for rare or serious adverse effects that might not have been fully detected prior to drug approval. The FDA must constantly balance the need to get a medically useful drug to the market quickly against the realization that the safety of the consumer is at stake. A good example of this is the testing and approval of new drugs for the treatment of the human immunodeficiency virus (HIV).

Controversy

The cost to the pharmaceutical industry of developing a new drug is estimated to be between $1.3 billion and $1.7 billion, although this figure has generated quite a bit of debate since this study was funded by pharmaceutical manufacturers. The relationship between drugs and high health-care costs is a topic of frequent public and political debate. High pharmaceutical costs lead some patients to make questionable cost-saving decisions, such as buying drugs from overseas vendors using the Internet or simply not taking their prescribed medicines.

Describe the process a new drug must undergo for approval. Several ethical, moral, and legal issues are implied in the preceding section on drug development. Can you expand upon them? Can you think of others?

1.3 HERBAL SUPPLEMENTS (NEUTRACEUTICALS)

The use of supplements, also called herbals, is growing in popularity. Frequently patients self-medicate with herbals, and health-care professionals are not even aware of it unless they ask. The FDA treats herbals as dietary supplements, and standards for supplements are different than those for drugs. The long and short of it is that, for herbal products, the manufacturer does not have to prove a product's safety and effectiveness before it is marketed. A manufacturer is allowed to say that a supplement helps a nutrient deficiency, supports health, or is tied to a particular body function (e.g., immunity) if there is research supporting this claim. A claim must be followed by the words "This statement has not been evaluated by the FDA. This product is not intended to diagnose, treat, cure, or prevent any disease." You can visit the National Institutes of Health (NIH) National Center for Complementary and Alternative Medicine for more information.

Patient & Family Education

Herbal Interactions

Herbs, vitamins, minerals, and certain other products taken by mouth and not regulated as drugs by the FDA are called "dietary supplements." Manufacturers and distributors do not need FDA approval to sell their dietary supplements. It is a good idea to encourage patients to check with their doctor or pharmacist prior to taking dietary supplements to make sure the supplements won't interfere with their other medical problems or medications.

One good example of why it is important to check with a health professional prior to taking dietary supplements can be illustrated by St. John's wort. This product is a dietary supplement that has been used by people with depression. But combining St. John's wort with certain HIV drugs significantly reduces their effectiveness and may also reduce the effectiveness of prescription drugs for heart disease, seizures, certain cancers, oral contraceptives, and depression.

1.4 DRUG INFORMATION SOURCES

Clinical pearl

The United States Pharmacopeia (USP) is the official organization that is responsible for establishing drug standards for the United States. (www.usp.org/aboutusp)

All health-care professionals must recognize the limitations of their knowledge and know where to find information about drugs. Depending on your workplace, a variety of drug references should be accessible to you. Good drug references and sources, in the authors' opinion, include the *American Hospital Formulary Service* (AHFS); *Drug Information,* by the American Society of Health System Pharmacists; and *Drug Facts and Comparisons,* by the Wolters Kluwer Company. *Drug Facts and Comparisons* has useful tables comparing drugs within a class. AHFS provides more information than drug package inserts. For example it lists unapproved medical indications. The PDR, or *Physicians' Desk Reference,* is useful if you are looking for product information required by the FDA, such as drug name, clinical pharmacology, indications, contraindications, drug interactions, adverse drug reactions, dosage, and administration.

Smartphone versions of the above references as well as several others are also available to health-care practitioners. LexiDrugs, ePocrates, and mobile-MICROMEDEX are several popular electronic drug references. These products vary considerably in terms of the type of drug information provided and cost.

As technology changes and new drugs are developed, you have a responsibility to update your knowledge. No one would deny that this is a formidable task. All you need to do is look at the size of the old PDRs compared with today's. The drug information you learn in school is frequently replaced with new concepts once you are out in practice. This requires that you devise a method of updating your knowledge through self-directed learning and continuing education.

CONTROVERSY

Prescribing patterns and treatments can change daily in response to new research published in medical journals, especially for drug therapy. What would you do if the prescriber were not incorporating the latest research findings into patient treatment?

1.5 INTERPRETING DRUG INFORMATION

Finding a good, valid source of drug information is the first step. Understanding and interpreting the information presented is the next step before one can apply this knowledge in drug administration and evaluation. Some of the typical information presented will include the drug name(s), the clinical pharmacology of how it works, indications and usage, contraindications, drug interactions, adverse reactions, and dosage and administration. We will discuss each of these categories by elaborating upon the specific sections contained in a drug package insert.

1.5a Drug Names

One of the most complicated factors for students encountering a drug for the first time is that it has not one name but at least two—and frequently more. Drugs have chemical names that describe the structure. An example is [4S-(4α,4aα,5aα,6α,12aα,)]-4-(di-methylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,6,10,12,12a-penthydroxy-6-methyl-1,11-dioxo-2-naphthacenecarboxamide. Imagine asking for that at your local pharmacy! The chemical name is important as a point of reference to manufacture the drug, but it has little practical use for the practitioner or consumer. Minor chemical changes in a drug can greatly change pharmacologic activity. This lesson has been learned the hard way by drug abusers in home labs creating designer drugs that turn out to have dangerous side effects.

Drugs are also assigned generic names by the United States Adopted Name (USAN) Council. The generic name for the previously given chemical name is tetracycline hydrochloride. Generic names are not owned by any particular pharmaceutical company and therefore are considered the nonproprietary name.

Once a drug is approved, a particular pharmaceutical company can produce and market it under its brand or trade name. The company that originally discovered the drug owns the trade name, which is derived with the help of creative marketing people. The trade name often relates to some aspect of either the generic name or the drug itself. For example, Sudafed is the trade name for the generic drug pseudoephedrine. Some other examples of innovative names are Theo-24 and Elixophyllin. Seeing "24" in the name, you can guess the dosage frequency—once a day, or once every 24 hours. From "Elixo" you can hypothesize that the drug is a liquid (a play on the word *elixir*; elixirs contain alcohol, which aids in dissolving the medicine). Names frequently give clues to drug indications—for example Flovent, for increasing air flow and ventilation. See Figure 1-1 for a portion of a drug package insert related to drug names for the bronchodilator Proventil® HFA.

Learning Hint

Trade names are traditionally capitalized and may carry a registered trademark symbol—®.

Learning Hint

Many drugs in a class have generic names that end in the same syllable (e.g., beta-blockers: propranolol, metoprolol, atenolol). Traditionally, generic names are written in all lowercase letters.

Clinical pearl

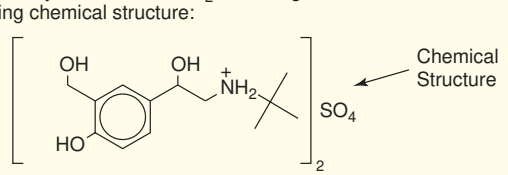
Drugs may have more than one name. This is because after the patent on the registered trademark expires, a generic drug product containing the same drug and dosage form can be developed by different drug companies. This is why we have both generic and brand names for many drugs.

FIGURE 1-1 Portion of Drug Package Insert Related to Drug Names

Trade Name → **PROVENTIL® HFA**
Generic Name → **(albuterol sulfate)**
Inhalation Aerosol

FOR ORAL INHALATION ONLY
Prescribing Information

Chemical Name → DESCRIPTION The active component of PROVENTIL© HFA (albuterol sulfate) Inhalation Aerosol is albuterol sulfate, USP racemic α^1 [(*tert*-Butylamino)methyl]-4-hydroxy-*m*-xylene-α,α′-diol sulfate (2:1)(salt), a relatively selective beta$_2$-adrenergic bronchodilator having the following chemical structure:



Albuterol sulfate is the official generic name in the United States. The World Health Organization's recommended name for the drug is salbutamol sulfate. The molecular weight of albuterol sulfate is 576.7, and the empirical formula is $(C_{13}H_{21}NO_3)_2 \cdot H_2SO_4$. Albuterol sulfate is a white to off-white crystalline solid. It is soluble in water and slightly soluble in ethanol. PROVENTIL HFA Inhalation Aerosol is a pressurized metered-dose aerosol unit for oral Inhalation. It contains a microcrystalline suspension of albuterol sulfate in propellant HFA-134a (1,1,1,2-tetrafluoroethane), ethanol, and oleic acid.

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1.5b Clinical Pharmacology

In the clinical pharmacology section of the drug insert information, you can learn about the mechanism of action of the drug and its specific classification. More on these topics will be covered in the upcoming pharmacokinetics section and in each specific chapter covering the various categories of drugs. See Figure 1-2 for the clinical pharmacology section of the drug package insert for Proventil® HFA.

FIGURE 1-2 Portion of Drug Package Insert Related to Clinical Pharmacology for the Drug Proventil® HFA

CLINICAL PHARMACOLOGY

Mechanism of Action *In vitro* studies and *in vivo* pharmacologic studies have demonstrated that albuterol has a preferential effect on beta$_2$–adrenergic receptors compared with isoproterenol. While it is recognized that beta$_2$–adrenergic receptors are the predominant receptors on bronchial smooth muscle, data indicate that there is a population of beta$_2$–receptors in the human heart existing in a concentration between 10% and 50% of cardiac beta-adrenergic receptors. The precise function of these receptors has not been established (see **WARNINGS, Cardiovascular Effects** section).

Activation of beta$_2$–adrenergic receptors on airway smooth muscle leads to the activation of adenylcyclase and to an increase in the intracellular concentration of cyclic-3', 5'-adenosine monophosphate (cyclic AMP). This increase of cyclic AMP leads to the activation of protein kinase A, which inhibits the phosphorylation of myosin and lowers intracellular ionic calcium concentrations, resulting in relaxation. Albuterol relaxes the smooth muscles of all airways, from the trachea to the terminal bronchioles. Albuterol acts as a functional antagonist to relax the airway irrespective of the spasmogen involved, thus protecting against all bronchoconstrictor challenges. Increased cyclic AMP concentrations are also associated with the inhibition of release of mediators from mast cells in the airway.

Albuterol has been shown in most clinical trials to have more effect on the respiratory tract, in the form of bronchial smooth muscle relaxation, than isoproterenol at comparable doses while producing fewer cardiovascular effects. Controlled clinical studies and other clinical experience have shown that inhaled albuterol, like other beta-adrenergic agonist drugs, can produce a significant cardiovascular effect in some patients, as measured by pulse rate, blood pressure, symptoms, and/or electrocardiographic changes.

Preclinical Intravenous studies in rats with albuterol sulfate have demonstrated that albuterol crosses the blood-brain barrier and reaches brain concentrations amounting to approximately 5% of the plasma concentrations. In structures outside the blood-brain barrier (pineal and pituitary glands), albuterol concentrations were found to be 100 times those in the whole brain.

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1.5c Indications and Usage

The indications and usage section will inform you of the FDA-approved clinical indication(s)—that is, why you would consider using this particular medication. However one should note that sometimes drugs are prescribed for uses not listed as an indication in the drug package insert. This is termed *off-label* use. See Figure 1-3 for the indications and usage section of the drug package insert for Proventil® HFA.

FIGURE 1-3 Portion of Drug Package Insert Related to Indications and Usage for the Drug Proventil® HFA

INDICATIONS AND USAGE

PROVENTIL® HFA Inhalation Aerosol is indicated in adults and children 4 years of age and older for the treatment or prevention of bronchospasm with reversible obstructive airway disease and for the prevention of exercise-induced bronchospasm.

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1.5d Contraindications

The contraindications section contains warnings as to particular patients or situations in which you should not use this medication. This section may also list precautions to follow when administering this drug or situations that may warrant closer patient monitoring. See Figure 1-4 for the contraindications section of the drug package insert for Proventil® HFA.

FIGURE 1-4 Portion of Drug Package Insert Related to Contraindications for the Drug Proventil® HFA

CONTRAINDICATIONS

PROVENTIL® HFA Inhalation Aerosol is contraindicated in patients with a history of hypersensitivity to albuterol or any other PROVENTIL HFA components.

WARNINGS

1. Paradoxical Bronchospasm: Inhaled albuterol sulfate can produce paradoxical bronchospasm that may be life threatening. If paradoxical bronchospasm occurs, PROVENTIL® HFA Inhalation Aerosol should be discontinued immediately and alternative therapy instituted. It should be recognized that paradoxical bronchospasm, when associated with inhaled formulations, frequently occurs with the first use of a new canister.
2. Deterioration of Asthma: Asthma may deteriorate acutely over a period of hours or chronically over several days or longer. If the patient needs more doses of PROVENTIL HFA Inhalation Aerosol than usual, this may be a marker of destabilization of asthma and requires re-evaluation of the patient and treatment regimen, giving special consideration to the possible need for anti-inflammatory treatment, eg, corticosteroids.
3. Use of Anti-Inflammatory Agents: The use of beta-adrenergic agonist bronchodilators alone may not be adequate to control asthma in many patients. Early consideration should be given to adding anti-inflammatory agents, eg, corticosteroids, to the therapeutic regimen.
4. Cardiovascular Effects: PROVENTIL HFA Inhalation Aerosol, like other beta-adrenergic agonists, can produce clinically significant cardiovascular effects in some patients as measured by pulse rate, blood pressure, and/or symptoms. Although such effects are uncommon after administration of PROVENTIL HFA Inhalation Aerosol at recommended doses, if they occur, the drug may need to be discontinued. In addition, beta-agonists have been reported to produce ECG changes, such as flattening of the T wave, prolongation of the QT_c interval, and ST segment depression. The clinical significance of these findings is unknown. Therefore, PROVENTIL HFA Inhalation Aerosol, like all sympathomimetic amines, should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension.
5. Do Not Exceed Recommended Dose: Fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs in patients with asthma. The exact cause of death is unknown, but cardiac arrest following an unexpected development of a severe acute asthmatic crisis and subsequent hypoxia is suspected.
6. Immediate Hypersensitivity Reactions: Immediate hypersensitivity reactions may occur after administration of albuterol sulfate, as demonstrated by rare cases of urticaria, angioedema, rash, bronchospasm, anaphylaxis, and oropharyngeal edema.

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What is the difference between a generic name and a brand name? What is the difference between an indication and a contraindication?

1.5e Drug Interactions

Often a patient is receiving more than just a single drug, and there is a potential for two or more drugs to interact. Drug interactions can result in unwanted or dangerous side effects by either reducing or increasing the action of one or more of the drugs involved. This usually happens by either increasing or decreasing a drug's absorption or elimination from the body. For example psyllium and digoxin, when given concurrently, will bind together within the stomach and cause a reduction in the amount of digoxin absorbed into the circulation. Therefore, the digoxin may not work as well as expected. Cimetidine is known for inhibiting the liver enzymes that metabolize some drugs. Patients may show increased effects of other drugs they may be taking because now these drugs may not be broken down or metabolized as readily. Phenytoin may increase the metabolism by the liver of certain medications, which would result in a decreased effect of the affected medications. Consulting up-to-date drug interaction information is important both to see if an interaction is possible and then to try and determine its significance.

Drug interactions usually carry a negative connotation among health professionals, but they are not always bad. Sometimes drug interactions can be beneficial. Ritonavir is a medicine used in combination with other HIV medicines only to boost the effect of the concurrently taken drug. This results in fewer pills and a reduction in the number of times per day a patient would need to take his or her HIV medicines. This hopefully also boosts compliance with the prescribed regimen, which is critical since there currently is no cure for HIV-infected individuals.

There are terms related to therapeutic drug interactions. When two drugs are given together and the result of those two can be summed up by the equation 1 + 1 = 2, the interaction is **additive**. Additive means that the sum of the effects of two drugs given together is equal to each of them given separately but at the same time. This can be beneficial when, for example, you are treating a patient with high blood pressure and you want to avoid the side effects that may occur with high doses of one drug. You can instead give lower doses of two drugs and rely on the additive hypotensive effects being equal to the single drug at a higher dose.

In some cases, giving two drugs together can result in a greater effect than would be expected by giving them together. When two drugs are given together and interact to equal 1 + 1 = 3, then **synergism** is occurring. Though it is mathematically incorrect, this expression describes the summation of the drug activity exceeding the sum of the two individual drugs. This can be very beneficial in the case of treatment of an infection with a combination of antibiotics. For example, when used together, the antimicrobials rifampin and nafcillin are effective in treating staphylococci; but when patients have joint-replacement infections (e.g., knee or hip), if we were to use one of these drugs alone, it would be ineffective in curing the infection.

If you really want to drive mathematicians crazy, **potentiation** can be described numerically as 1 + 0 = 3. This means that one of the drugs or substances, while having no direct effect, nevertheless increases the response of the other drug, which normally has a lesser effect. Grapefruit juice, when consumed by patients taking felodipine (medicine for high blood pressure), may lead to a dangerous drop in blood pressure. Grapefruit juice inhibits the metabolism of felodipine in the intestine resulting in a 50%–250% increase in the plasma concentration of felodipine. You can see how this could be confused with synergism, yet it is not synonymous. See Figure 1-5, which shows the drug interactions section of the drug package insert for Proventil® HFA.

Sometimes a drug will have a completely unpredicted or "off-the-wall" effect. This is termed an *idiosyncratic* reaction.

Clinical pearl

The fact that these common drugs are considered "red flag" drugs does not mean that they should not be administered. It simply means that more attention should be paid to the potential for their interaction with other drugs the patient may have been prescribed.

FIGURE 1-5 Portion of Drug Package Insert Related to Drug Interactions for the Drug Proventil® HFA

Drug Interactions

1. Beta-Blockers: Beta-adrenergic-receptor blocking agents not only block the pulmonary effect of beta-agonists, such as PROVENTIL® HFA Inhalation Aerosol, but may produce severe bronchospasm in asthmatic patients. Therefore, patients with asthma should not normally be treated with beta-blockers. However, under certain circumstances, eg, as prophylaxis after myocardial infarction, there may be no acceptable alternatives to the use of beta-adrenergic blocking agents in patients with asthma. In this setting, cardioselective beta-blockers should be considered, although they should be administered with caution.

2. Diuretics: The ECG changes and/or hypokalemia which may result from the administration of nonpotassium-sparing diuretics (such as loop or thiazide diuretics) can be acutely worsened by beta-agonists, especially when the recommended dose of the beta-agonist is exceeded. Although the clinical significance of these effects is not known, caution is advised in the coadministration of beta-agonists with nonpotassium-sparing diuretics.

3. Albuterol-Digoxin: Mean decreases of 16% and 22% in serum digoxin levels were demonstrated after single-dose intravenous and oral administration of albuterol, respectively, to normal volunteers who had received digoxin for 10 days. The clinical significance of these findings for patients with obstructive airway disease who are receiving albuterol and digoxin on a chronic basis is unclear, nevertheless, it would be prudent to carefully evaluate the serum digoxin levels in patients who are currently receiving digoxin and albuterol.

4. Monoamine Oxidase Inhibitors or Tricyclic Antidepressants: PROVENTIL® HFA Inhalation Aerosol should be administered with extreme caution to patients being treated with monoamine oxidase inhibitors or tricyclic antidepressants, or within 2 weeks of discontinuation of such agents, because the action of albuterol on the cardiovascular system may be potentiated.

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Some drugs are at higher risk of causing drug interactions, and some patients are at higher risk of experiencing drug interactions. Certain drugs are known to be at high risk of causing drug interactions and are even considered to be "red flag" drugs. See Table 1-1, which lists some major red flag drugs.

***TABLE 1-1* "Red Flag" Drugs**

Drug Name
warfarin
cimetidine
aspirin
phenytoin
theophylline

Clinical pearl

With the recent push to get drugs approved faster and on the market sooner, serious ADRs may not be detected until postmarketing surveillance. Enrolling enough patients in research studies to detect all ADRs before FDA approval is not feasible, so rare ADRs may not be detected until there is widespread use of a drug in a large population.

1.5f Adverse Drug Reactions

Not only can drugs interact with each other, but they may also have unintended interactions within the human body. Contrary to the Hippocratic Oath—which says, "First, do no harm"—at least 5% of reported hospitalizations are the result of an **adverse drug reaction** (ADR). When patients experience unintended side effects from medication, they are having ADRs. Such reactions also occur in patients who are already in the hospital, which can then result in an increased length of stay. Adverse drug reactions can range from a side effect that is mild and goes away with repeated use or discontinuation to a more severe or life-threatening reaction.

One can easily confuse the terms *ADR* and *drug allergy* and mistakenly use the terms synonymously. ADRs include many things, such as tremors, bronchospasms, headaches, changes in laboratory results of renal function, photosensitivity, and

so on. An allergy or hypersensitivity is only one example of an ADR, and not all ADRs are allergies. Drug allergies induce a hypersensitivity reaction. This reaction can vary in severity and can be thought of as a continuum. Allergies can be acute and life-threatening—as, for example, in anaphylactic shock—or can be found on the milder end of the continuum, for example, as a dermatologic rash such as hives. See Figure 1-6 for the ADR section of the drug insert for Proventil® HFA.

FIGURE 1-6 Portion of Drug Package Insert Related to Adverse Reactions for the Drug Proventil® HFA

ADVERSE REACTIONS

Adverse reaction information concerning PROVENTIL® HFA Inhalation Aerosol is derived from a 12-week, double-blind, double-dummy study which compared PROVENTIL HFA Inhalation Aerosol, a CFC 11/12 propelled albuterol inhaler, and an HFA-134a placebo inhaler in 565 asthmatic patients. The following table lists the incidence of all adverse events (whether considered by the investigator drug related or unrelated to drug) from this study which occurred at a rate of 3% or greater in the PROVENTIL HFA Inhalation Aerosol treatment group and more frequently in the PROVENTIL HFA Inhalation Aerosol treatment group than in the placebo group. Overall, the incidence and nature of the adverse reactions reported for PROVENTIL HFA Inhalation Aerosol and a CFC 11/12 propelled albuterol inhaler were comparable.

Adverse Experience Incidences (% of patients) in a Large 12-week Clinical Trial*

Body System/Adverse Event (Preferred Term)		PROVENTIL® HFA Inhalation Aerosol (N = 193)	CFC 11/12 Propelled Albuterol Inhaler (N = 186)	HFA-134a Placebo Inhaler (N = 186)
Application Site Disorders	Inhalation Site Sensation	6	9	2
	Inhalation Taste Sensation	4	3	3
Body as a Whole	Allergic Reaction/Symptoms	6	4	<1
	Back Pain	4	2	3
	Fever	6	2	5
Central and Peripheral Nervous System	Tremor	7	8	2
Gastrointestinal System	Nausea	10	9	5
	Vomiting	7	2	3
Heart Rate and Rhythm Disorder	Tachycardia	7	2	<1
Psychiatric Disorders	Nervousness	7	9	3
Respiratory System Disorders	Respiratory Disorder (unspecified)	6	4	5
	Rhinitis	16	22	14
	Upper Resp Tract Infection	21	20	18
Urinary System Disorder	Urinary Tract Infection	3	4	2

*This table includes all adverse events (whether considered by the investigator drug related or unrelated to drug) which occurred at an incidence rate of at least 3.0% in the PROVENTIL HFA Inhalation Aerosol group and more frequently in the PROVENTIL HFA Inhalation Aerosol group than in the HFA-134a placebo inhaler group.

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Knowledge of ADRs in select populations, such as pregnant women, would be especially useful. However, enrolling pregnant patients in research is not always ethical. Consequently information on how drugs may adversely affect the fetus is not always known or reported. Absorption, one of the concepts of pharmacokinetics to be discussed later in this chapter, needs to be considered when discussing pregnancy and ADRs. When you think of drug absorption for women of childbearing age, it is safest to assume that any drug given to a pregnant woman may also be given to the baby and may be crossing the fetal-placental barrier. The same applies to lactating women, with drugs passing from breast milk to the baby.

A drug that has the potential to damage a fetus in utero when administered to a pregnant woman is called **teratogenic**. The teratogenicity of drugs is classified based on risk and the limited data available. For example, drugs that have shown evidence of fetal risk that outweighs any possible benefit are considered "category X" and are

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absolutely contraindicated. For other drugs, including some for asthma and other chronic diseases such as epilepsy, the risks to the baby caused by the mother not having her disease controlled with a drug can outweigh the risks of drug exposure for the baby. Decisions about drug use in pregnant women need to be made mutually by the patient and the health-care provider.

What is the difference between an allergy and an ADR?

Some of the most serious ADRs with cardiopulmonary implications are reactions such as acute pulmonary edema, bronchial asthma, pulmonary fibrosis, or respiratory muscle impairment affecting the patient's ability to ventilate. Some of these reactions may occur due to a direct cytotoxic effect on alveolar endothelial cells and can severely impair the vital process of gas exchange. More than 150 drugs have been shown to produce pulmonary ADRs, and Table 1-2 lists some examples of drug-induced pulmonary adverse reactions.

TABLE 1-2 **Drug-Induced Pulmonary ADRs**

ADR	Drug
Pulmonary edema	methadone IV fluids epinephrine hydrochlorothiazide salicylates
Pulmonary fibrosis	amiodarone busulfan nitrofurantoin
Respiratory muscle impairment	alcohol corticosteroids sedatives penicillamine
Bronchospasm	ACE inhibitors beta-blockers nonsteroidal anti-inflammatory drugs (NSAIDs)

There are also other possible pulmonary complications. Angiotensin-converting enzyme (ACE) inhibitors for the heart, as discussed further in Chapter 9, cause a cough in up to 15% of patients treated. Plain aspirin, which you can buy over the counter (OTC) without a prescription, can cause bronchospasms in up to 20% of patients with asthma. Even topical beta-blocker eye drops can be absorbed enough to aggravate chronic obstructive pulmonary disease (COPD).

1.5g Dosage and Administration

The dosage and administration section of the drug package insert describes the standard dose for the medication. In addition, it should elaborate on how the medication is supplied and whether any special treatment or care should be given to preserve its effectiveness. This section describes the route of administration of the drug. The route of administration is such an important topic that it will be discussed separately in the upcoming section. Please see Figure 1-7 for the dosage and administration section of the drug package insert for Proventil® HFA.

FIGURE 1-7 Portion of Drug Package Insert Related to Dosage and Administration for the Drug Proventil® HFA

DOSAGE AND ADMINISTRATION

For treatment of acute episodes of bronchospasm or prevention of asthmatic symptoms, the usual dosage for adults and children 4 years of age and older is two inhalations repeated every 4 to 6 hours. More frequent administration or a larger number of inhalations is not recommended. In some patients, one inhalation every 4 hours may be sufficient. Each actuation of PROVENTIL® HFA Inhalation Aerosol delivers 108 mcg of albuterol sulfate (equivalent to 90 mcg of albuterol base) from the mouthpiece. It is recommended to prime the inhaler before using for the first time and in cases where the inhaler has not been used for more than 2 weeks by releasing four "test sprays" into the air, away from the face.

Exercise Induced Bronchospasm Prevention The usual dosage for adults and children 4 years of age and older is two inhalations 15 to 30 minutes before exercise.

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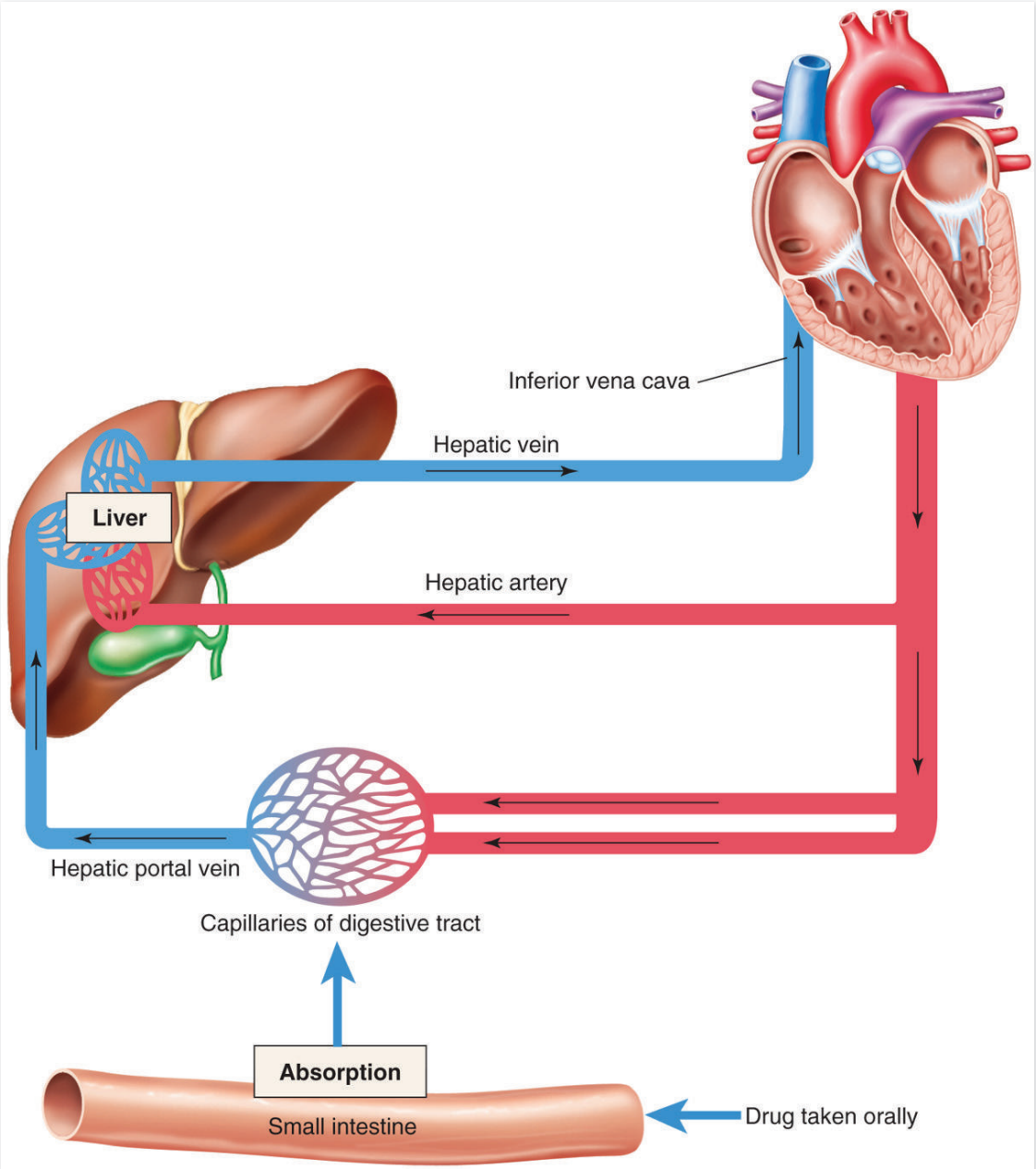
1.6 ROUTES OF ADMINISTRATION

One of the first mysteries of pharmacology is the simple and common question of why some drugs are given orally and others are given by a shot or even by other means. Routes of administration of drugs are selected according to the rate of onset of drug activity desired and physiochemical factors that affect drug absorption. For example, some drugs given by mouth undergo what is called a **first-pass effect**. After being absorbed, drugs with a first-pass effect do not go directly into the systemic circulation but instead go through the liver. In the liver the drug undergoes a metabolic change. The liver enzymes inactivate some of the drug before it reaches the blood circulation (see Figure 1-8). For this reason, the dosage of an orally administered drug may need to be higher than when it is administered by a route that bypasses the liver, such as the intravenous route. Drugs given via the **parenteral route** (by injection) can avoid the first-pass effect, which explains why doses of the same drug vary depending on the route of administration—for example, oral propranolol 40 mg versus 1 mg of the drug intravenously (IV). These two routes, with very different dosages, will produce about the same response.

FIGURE 1-8 The First-Pass Effect

Drugs administered orally are first absorbed through the small intestine and then enter the liver where they begin to be metabolized (broken down) before reaching the bloodstream.



The route of drug administration is also selected based on how compliant the patient is in taking prescribed medication regularly. For example, *depot formulations* of drugs given intramuscularly for noncompliant schizophrenic patients every 2 weeks can keep their disease controlled, whereas they may not take their prescribed oral medications consistently. Depot formulations are drugs that are slowly released once administered, so they only need to be given every week or so, depending on the drug. Some depot drugs are formulated in oil, which allows for slow release into the bloodstream. Depot birth control is an alternative for women who do not wish to get pregnant but who may be less compliant about using other forms of birth control.

1.6a Enteral Routes

Enteral routes of drug absorption are via the gastrointestinal tract for systemic purposes and include the oral (PO), sublingual (SL), nasogastric (NG) tube, percutaneous endoscopic gastrostomy (PEG) tube, and rectal (per rectum or PR) routes. The NG tube is inserted through the nose and esophagus and rests within the stomach. The PEG tube is inserted directly into the stomach. The oral route is usually considered the most common and convenient route. **Sublingual** drugs are absorbed quickly owing to the rich vasculature under the tongue, which explains why this route is chosen for nitroglycerin for quick relief of cardiac chest pain. Rectal drug administration can be very effective for patients ordered "nothing by mouth" (NPO) or those who are vomiting or unable to swallow oral medications. Patients who are receiving enteral nutrition via a gastric tube are frequently given drugs through that tube as well, as long as drug stability and compatibility in mixing with foods and liquids are taken into consideration.

Learning Hint

PO is Latin for *per os*, which means "through the mouth."

1.6b Parenteral Routes

Parenteral routes include the injectable routes. They may be through central lines, intra-arterial, intravenous (IV), intramuscular (IM), or subcutaneous routes (SC). Drugs given parenterally go right into the bloodstream and absorption is rapid, so this route is desirable for emergency situations when an immediate response is needed. Drugs that are insoluble and cannot be dissolved cannot be given intravenously. Some drugs cannot be administered together intravenously because of physical incompatibilities. There are thick reference books dedicated to describing which drugs are compatible with each other in solution.

The rate for IM drug absorption depends on the formulation used. Clear or water-based solutions have a rapid effect. Suspensions that are cloudy or oil-based have a slower rate of absorption. Parenteral administration carries with it the risk of infection, pain, or local irritation.

Learning Hint

The term *parenteral* is derived from the Greek *para*, "apart from," plus *enteron*, "intestine," and technically means any route outside of the oral and intestinal tract. Clinically, it refers to the injectable routes.

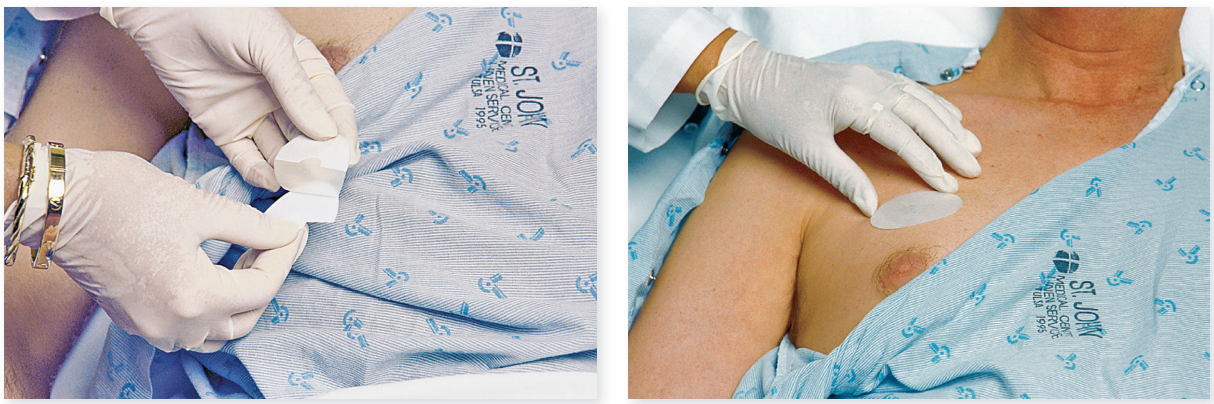
1.6c Other Routes

Topical drugs are administered onto the skin or mucous membranes. Examples include nitroglycerin ointment and skin creams. *Inhalation* drug delivery is a form of topical delivery to the lungs that may avoid systemic side effects. *Inhalation* drug therapy or medicated aerosol therapy delivers micron-sized aerosol particles through the bronchial tree to the lungs, providing for rapid absorption. Local administration of a drug to the lungs is advantageous because of their large surface area and location close to the pulmonary circulation. It is also so important in cardiopulmonary pharmacotherapy that it warrants a whole chapter (Chapter 4).

Transdermal delivery of a drug occurs through a skin patch that allows the drug to be released slowly; this provides for sustained blood levels throughout the day without the patient having to remember to take medications (see Figure 1-9). Considering people's busy lives, drugs need to be dosed so they will not interfere with lifestyle, which may enhance compliance and keep drugs effective. See Table 1-3 for a summary of administration routes.

FIGURE 1-9 Transdermal Patch Administration

(a) protective covering removed; (b) patch applied to clean, dry, hairless skin and labeled with date, time, and initials.



(a) (b)

Source: Pearson

TABLE 1-3 Examples of Drug Administration Routes

Route	Major Points	Examples
Oral (PO)	May be enteric-coated, sustained-release, tablet, or capsule; some are crushable, some lose their potency when crushed; this is the most convenient and economical route	Most prescribed drugs and over-the-counter (OTC) medications
Sublingual (SL)	Provides quick onset with good salivary flow	Nitroglycerin
Rectal (PR)	Can be more convenient when patients cannot swallow (nausea/NPO)	Antinausea medications
Nasogastric (NG) tube	Be careful of drug stability and clogging up the tube	Nutritional feedings
Percutaneous endoscopic (PEG) tube	More comfortable than NG tube	Nutritional feeding and liquid medication; tablets or capsules that are not sustained release dosage forms
Intravenous (IV)	Use in quick onset, emergency situations, and long-term infusions	Emergency medications
Intramuscular (IM)	Once injected, there to stay—even if side effects occur	Iron
Transdermal	Is easier to remember because dosing is less frequent	Nicotine or nitroglycerin patches
Inhalational	Has fewer systemic side effects, requires coordination	Metered-dose inhalers (MDIs), dry-powder inhalers (DPIs) Small-volume nebulizers (SVNs)

1.7 PHARMACOKINETICS

Pharmacokinetics means the movement (kinesis) of the drug throughout our body. Pharmacokinetics is the study of what happens to the drug from the time it is put into the body until it has left the body. Pharmacokinetic principles help determine drug dosage in terms of amount, duration, and frequency. Pharmacokinetics includes the following processes: *absorption, distribution, metabolism,* and *elimination* of a drug (ADME for short). Absorption occurs when the drug passes from its administration site into plasma. Distribution determines where the drug goes once it is within the body. For any drug to work, it must be absorbed and distributed to an active site. Metabolism refers to biotransformation, in which drugs are converted to a water-soluble form for elimination. Elimination of a drug occurs by hepatic metabolism or renal excretion. Each of these components of pharmacokinetics will be broken down and discussed in a different section.

Learning Hint

Pharmacokinetics is often confused with pharmacodynamics. Pharmacokinetics is what the body does to the drug. Pharmacodynamics, on the other hand, is what the drug does to the body and will be discussed shortly.

1.7a Absorption

A drug must first be disintegrated or dissolved before it can be absorbed into the systemic circulation. The rate-limiting step in absorption is disintegration. If a drug does not have to disintegrate and is already in a solution, it will begin to work more quickly. Most injections of drugs (IM, subcutaneous, and intradermal) are absorbed from body tissues; only intravenous injections completely bypass the absorption step and directly enter the bloodstream.

Not all of the drug may even reach the bloodstream. **Bioavailability** measures the amount of drug that is absorbed into the circulation. Bioavailability is influenced by drug solubility, dosage form, route of administration, pH values, and salt form, to name a few factors. One example of this concept is how the pH (a measure of the acidity or alkalinity) of different parts of the gastrointestinal (GI) tract can affect the absorption and thus the bioavailability of the drug. Some drugs are permanently charged, but most are weak acids or bases whose ionization is affected by pH. In other words, the drug can exist in either its ionized or its nonionized form, depending on the pH values of surrounding fluids.

The important aspect of ionization is that the nonionized (no charge or neutral) drug is absorbed through membranes, so it can be active, while the ionized (charged) form of the drug is not. The stomach is very acidic, at pH 1–2, whereas the intestines are about pH 4–5; farther along the GI tract, the alkalinity increases. This means that drugs such as aspirin, which are more in their nonionized form at an acidic pH, are better absorbed in acidic environments such as the stomach. Alkaline drugs such as quinidine become more nonionized in alkalinic environments and are therefore better absorbed as they progress through the GI tract.

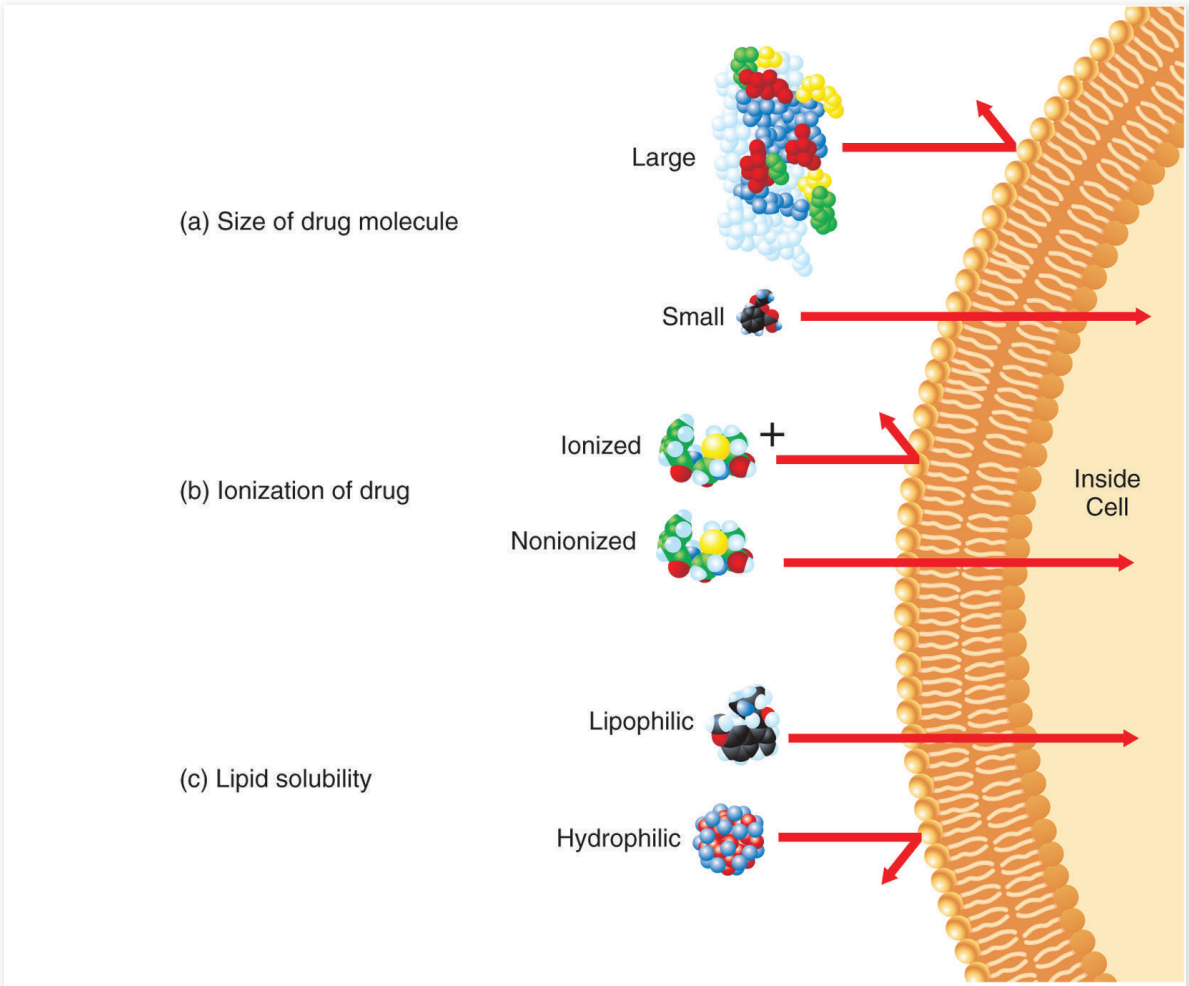
Clinical pearl

Specially coated (enteric) tablets are designed to resist being absorbed in the stomach, where they may be irritating to the stomach lining.

Ultimately, drugs must be absorbed through membranes to reach their site of action. Drugs can pass through some membranes but not all. Mechanisms by which drugs pass through membranes include passive diffusion, facilitated diffusion, active transport, and passage through ion channels. These transfer processes will be discussed in chapters where they are pertinent. See Figure 1-10, which shows factors such as drug molecule size, ionization, and lipid solubility and their effects on membrane passage.

FIGURE 1-10 Variables That Affect Passage of Drugs Across Plasma Membranes

(a) size of drug molecule, (b) ionization of drug, (c) lipid solubility across the lipid cell membrane.

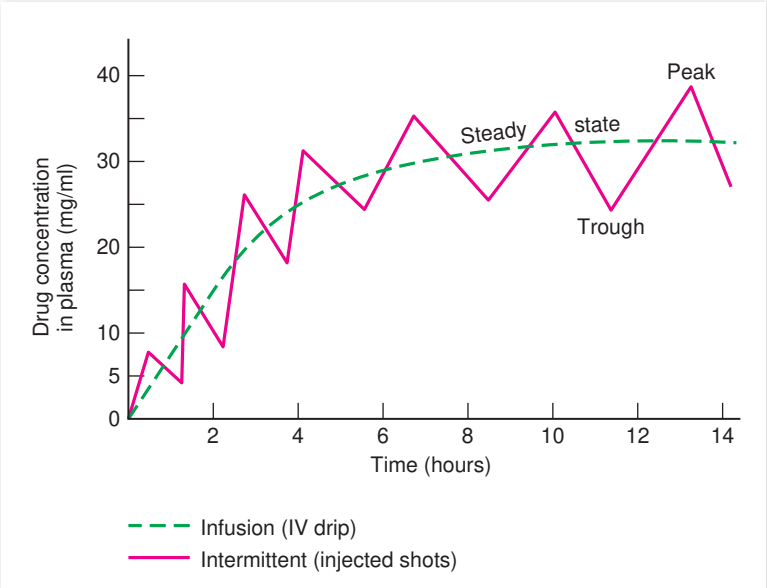


time for review

If you were in severe pain, would you rather have a morphine tablet or solution? Why?

Intravenous drug administration differs depending on whether the drug is given as a continuous infusion (IV drip) or as an intermittent dose (injected IV shot or bolus). A continuous infusion gives a regulated, consistent dosage over time without peaks and valleys in drug concentration. An intermittent intravenous dose has more peaks and troughs in drug concentration (see Figure 1-11).

FIGURE 1-11 Intermittent and Infusion Dosing



For some drugs, laboratory testing of blood levels is available to tell us whether an individual patient has enough drug in the blood to be effective or toxic. The effective blood level is considered the therapeutic blood level and has a defined **therapeutic range**. Below this level, the drug is likely less effective, and above this level, toxicity may result (see Table 1-4, which lists common drugs for which blood-level testing is available).

Clinical pearl

When testing blood levels, the timing of the blood draw relative to the dose is important for interpretation. Also, even if patients have identical serum drug concentrations, there may be different clinical responses among individuals.

TABLE 1-4 **Drugs with Blood-Level Tests and Therapeutic Ranges**

Drug Name	Therapeutic Range
theophylline	5–15 mcg/ml
digoxin	0.5–2 ng/ml
phenytoin	10–20 mcg/ml
lithium	0.6–1.2 meq/L
carbamazepine	4–12 mcg/ml
gentamicin	<2 mcg/ml
vancomycin	5–20 mcg/ml

1.7b Distribution

After absorption, the drug is distributed in the body. The major vehicle for distribution is via the bloodstream. As mentioned in the section on absorption, the drug must also distribute through membranes to reach certain active pharmacologic sites called receptors. Different drugs are able to distribute to different locations. The blood flow, fat, or water solubility of the drug and **protein binding** influence drug distribution.

Protein binding occurs when portions of the drug are bound to proteins in the bloodstream, such as albumin, and are thus unable to bind with active pharmacologic sites to have a desired effect. For example, if a person has low serum albumin (i.e., is malnourished), there is not as much protein for the drug

Clinical pearl

The rate of absorption may be proportional to the rate of blood flow at the site. Sometimes drugs are administered in combination with epinephrine, which is a vasoconstrictor. When epinephrine is given with a local anesthetic, such as lidocaine, the decreased blood flow from vasoconstriction keeps much of the drug at the desired site; this may therefore decrease the risk of systemic side effects when just a local effect is desired.

to bind to; therefore, much of the drug will be free in the bloodstream. Because free, unbound drug is active drug, a patient with low albumin may have higher blood levels of free, active drug than someone with normal albumin and will show a greater drug response.

Drugs differ in their percentage of protein binding. The PDR includes information on protein-binding percentages. Knowledge of protein binding is important because protein-binding displacement is one mechanism by which drugs interact with each other. If there are only so many proteins for a drug to bind to and another drug is added to a patient whose proteins are already bound by a previous drug, the drugs will compete for placement on the protein. The one that is not bound will be free to find an active receptor site.

Volume of distribution (VD) describes the areas in the body where drugs can be distributed. Fat-soluble (lipophilic) drugs pass through fat more easily than through water. Fat-soluble drugs have an increased effect in patients with more fat, and water-soluble drugs have an increased effect in those with larger water compartments. Fat and water compartments change with age and are one explanation for why different doses may be needed in young and elderly patients. For example, the sedative diazepam (Valium®) is a fat-soluble drug. Obese patients may be sedated longer on a given dose of diazepam than lean patients.

1.7c Metabolism

After a drug has been absorbed and distributed, metabolism occurs because the body works to get rid of anything foreign. Before a drug can be excreted, it usually has to be metabolized so that it becomes more water-soluble and more able to leave the body via urine, feces, or sweat. The drug is broken down into several components or metabolites. Some metabolites of a drug are active and others are not. Metabolism may occur by means of chemical reactions, such as oxidation, conjugation, acetylation, or glucuronidation, to name a few.

One of the major organs for drug metabolism is the liver. The liver has a microsomal drug oxidation system called the cytochrome P450 system, which is responsible for metabolizing many drugs. These enzymes can be induced (increased in activity) or inhibited (decreased in activity). This is a common mechanism for drug interactions. Enzyme induction may explain why patients who drink alcohol frequently are more tolerant of the effects of alcohol—because the alcohol may be metabolized more quickly.

Drug doses can change depending on whether the liver enzymes are inducing or inhibiting, and there is no easy way to know other than to be aware of drugs that affect enzymes. See Table 1-5 for drugs that affect liver enzymes.

Some races have an increased frequency of a genetic deficiency of the enzyme that metabolizes alcohol and are therefore more susceptible to its effects. The field of research that studies genetic differences in drug response is called pharmacogenomics.

TABLE 1-5 Drugs That Affect Liver Enzymes

Inducers	Inhibitors
barbiturates	cimetidine
phenytoin	disulfuram
carbamazepine	allopurinol
rifampin	influenza vaccine

There is no good way to predict the liver's ability to metabolize drugs in a given patient. Some patients genetically lack enzymes to metabolize certain

drugs. In addition, lab tests of liver function do not correlate with the body's ability to metabolize a drug, and elimination in the liver cannot be assessed quantitatively. Liver disease may indicate that a particular drug should not be used or should be dosed differently. Because the liver is a site of drug metabolism, it is also susceptible to drug-induced toxicity. More than 600 drugs have been associated with drug-induced liver toxicity. Alcohol and acetaminophen are two common ones, especially when used in combination.

Life Span Considerations

Age and Its Effect on Metabolism

Drug metabolism in children may be reduced at birth and mature along with age. The fetal liver has about one-third the drug metabolism capacity of the adult liver.

Drug metabolism in the elderly may be affected both by underlying diseases and by advancing age. Advancing age alone results in a reduction in liver mass by about 20%–30%. As a result of these changes, drug metabolism that depends on the liver may be reduced in the elderly. This may result in an exaggerated clinical response or intolerable adverse effects (e.g., propranolol causing severe bradycardia or an excessive feeling of tiredness). In general, this is why the dosages of drugs are usually reduced in children and the elderly.

1.7d Elimination

The last component of pharmacokinetics is elimination. Some drugs are eliminated after they are metabolized, and others are excreted unchanged in the urine. Still others are eliminated in feces or even through the skin or pulmonary system. Inhalation anesthesia requires that the gas pass from inspired air to the blood and brain. Drug action is terminated when the drug is eliminated in the lungs.

Renal excretion rate is affected by glomerular filtration, tubular secretion, and tubular reabsorption. Impaired renal function can prolong the effects of drugs eliminated by the kidneys because they will not be readily eliminated and will remain longer in the system.

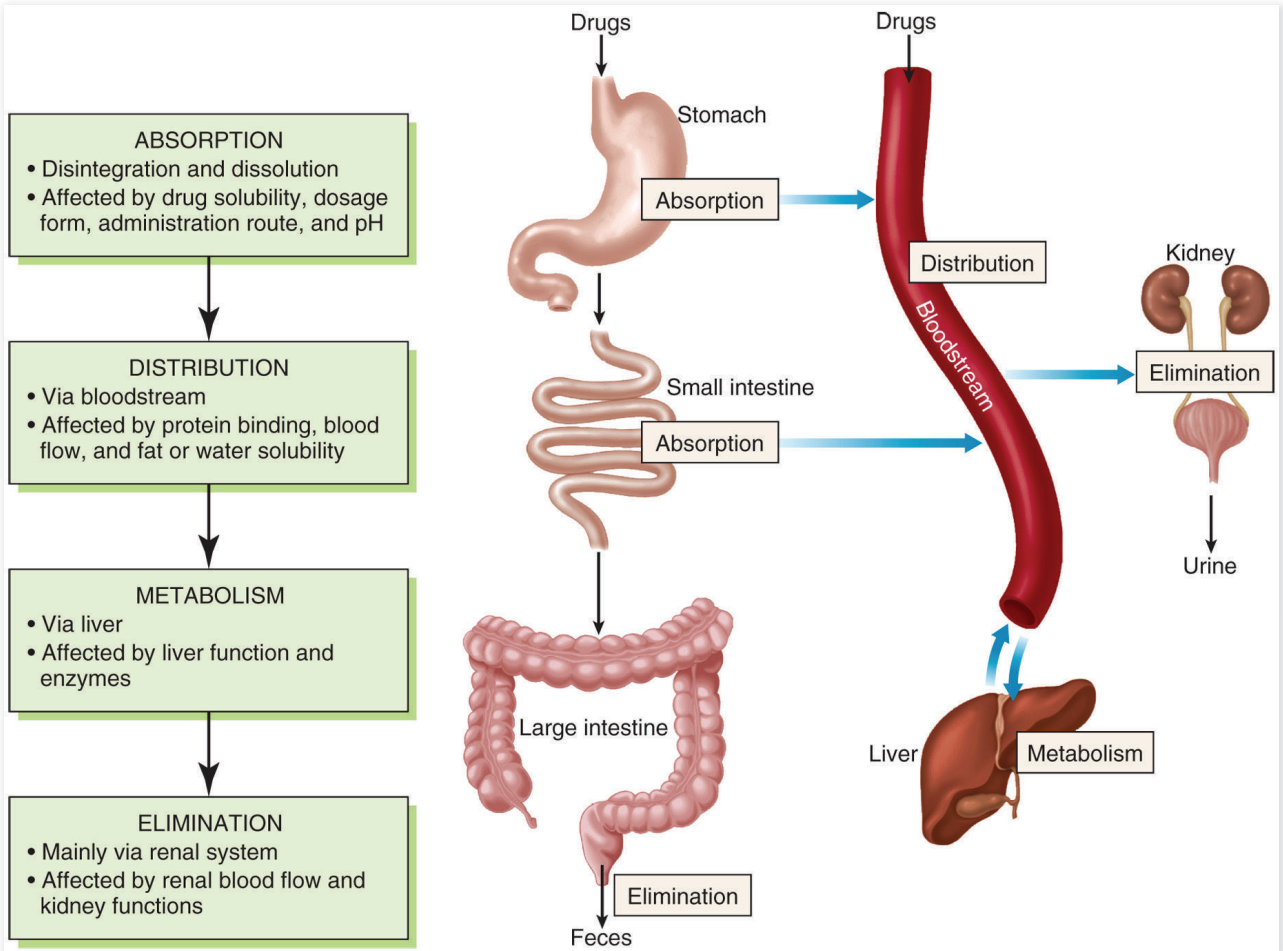
Because drugs can be excreted in the urine, urine testing is becoming more common in the workplace. Urine testing can be used to screen patients for drug abuse or for poisoning identification. Whether the drug is fat- or water-soluble influences how long after ingestion it may be detected in the urine. Urine testing and even saliva testing are useful to monitor patients in drug rehabilitation programs. Tests differ in sensitivity and specificity.

The alcohol breath test is used to assess intoxication for DUIs because ethanol is excreted in expired air. Urine screens are used in the workplace to detect past and current medication use on the basis of excretion of drug metabolites (breakdown products) in the urine.

Why would patients with kidney disease or decreased kidney function, such as the elderly, be prescribed lower doses of a medication?

Now that we have completed the discussion of pharmacokinetics, see Figure 1-12, which relates its four phases.

FIGURE 1-12 Pharmacokinetics: The Whole Picture



1.8 PHARMACODYNAMICS

As stated earlier, **pharmacodynamics** is what the drug does to the body. Once a drug is absorbed and distributed, drug action requires drug presence at a particular type of **receptor**. Receptors are targets for drugs; they are molecules located on the cell surface. This is where the action takes place. They are not, however, the only target for drugs; drugs also bind to carrier molecules and ion channels, for example—each of which will be discussed in upcoming chapters.

1.8a Selectivity

There are only so many receptors per cell and only certain kinds of receptors on different cells. Because most drugs produce several effects, **selectivity** refers to the extent to which a drug acts at one specific site or receptor. The more specific a drug can be on a particular cell or tissue, the more useful it is. Unfortunately, no drug acts with complete selectivity, which is why side effects occur. If you give a drug that kills a microorganism but it is not selective enough to avoid killing the

patient, then the drug is not selective enough to be useful. Another example is the search for drugs that kill only cancer cells, not all living cells.

A drug produces a particular effect by combining chemically with a receptor on which it acts. When a drug binds to a receptor, one of the following can happen:

(1) An ion channel is opened or closed.
Example: Calcium-channel blockers inhibit excess calcium from entering myocardial tissue.

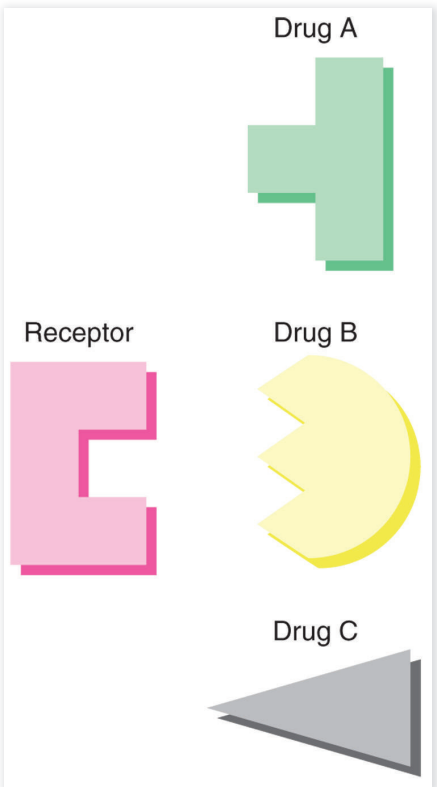
(2) Biochemical messengers are activated that initiate chemical reactions.
Example: Beta-adrenergic bronchodilators increase levels of cyclic 3,5-AMP, which causes smooth muscle relaxation.

(3) A normal cellular function is turned on or off.
Example: Antibiotics inhibit specific cellular functions that result in cell death.

1.8b Lock-and-Key Receptor Theory

A simplified description of interactions between drugs and receptors is the lock-and-key analogy. If the drug does not fit the receptor, no activity can occur. For example, current pain medications that have been derived from chemical variations of opium capitalize on this theory. Scientists worked with the lock-and-key theory to identify what parts of the chemical structure fit the receptor to cause analgesia and what parts cause side effects and dependence, and then they adjusted the chemistry to make more useful drugs. See Figure 1-13, which illustrates the lock-and-key theory.

FIGURE 1-13 The Lock-and-Key Receptor Theory: Which Drug Has Receptor Selectivity?



1.8c Racemic Mixtures

Many drugs are commercially available as a **racemic** mixture, meaning one that contains two different isomers. Isomers have the exact same chemical components, only bonded differently, and can be thought of as chemical mirror images. Another way of explaining this would be the fact that we have two hands. While they may not exactly be mirror images of each other, if you are right-handed, you can usually do more with this hand than your left. Each isomer usually has different activity or one is more potent than the other. An example is racemic epinephrine, which is made up of an L and a D isomer. The L isomer of epinephrine is 15 times more active than the D isomer. Isomer isolation is the target of a lot of pharmaceutical research, but the clinical importance is questionable—especially since the single-isomer products are more expensive. The single-isomer bronchodilator levalbuterol will be discussed further in Chapter 5.

1.8d Agonists Versus Antagonists

Learning Hint

The medical term *endo* means "within" and therefore refers to substances that are actually produced within the body, such as surfactants needed to keep the lungs open. *Exo* means "outside of"; exogenous surfactants are given to premature infants who are not producing endogenous surfactants.

The lock-and-key receptor theory explains the effects of chemicals on biologic systems. Drugs bind to cellular receptors according to their chemical structure, which starts biochemical reactions that can change cell physiology. The same explanation applies whether chemicals are endogenous (physiologically produced *within* the body) or exogenous (pharmacologically administered). However, drugs can bind with the receptor site and activate or block a response.

For example both **agonists** and **antagonists** can bind to a receptor; however, they differ in what they do once combined. Agonists are drugs with affinity for a receptor that cause a specific response. Affinity is the strength of binding between a drug and a receptor. Antagonists are also drugs with affinity for a receptor but have very little or no response when combined. Agonists activate the receptors. Antagonists combine at the same site but do not cause activation of the receptor. Drug antagonism can occur when the effect of one drug is lessened or blocked completely in the presence of another. An example of chemical antagonism is when protamine is used to neutralize the anticoagulant effects of heparin by forming an inactive heparin–protamine complex. This is desirable in cases of hemorrhage due to heparin overdoses for treatment of blood clots.

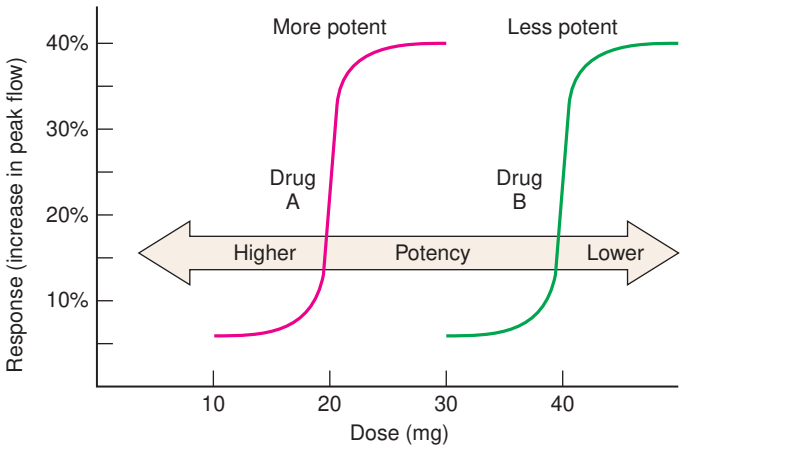
Drugs within a class differ in their affinity or likelihood of interacting with a receptor. If all drugs had to do was occupy a receptor to produce a pharmacologic effect, then all drugs acting on a receptor would produce the same effect. The reason this is not true is intrinsic activity, which can best be explained using numbers. Intrinsic activity is a measure of a drug's effectiveness in causing a response, or the **efficacy** of the drug at the receptor. For example, a drug with an intrinsic activity of 1 is a full agonist. A drug with an intrinsic activity of 0.5 is a partial agonist. An antagonist has intrinsic activity of 0 but does have affinity to bind. Both full and partial agonists want to bind to the receptor and thus have affinity, but a full agonist is more efficacious and causes a greater response.

1.8e Potency

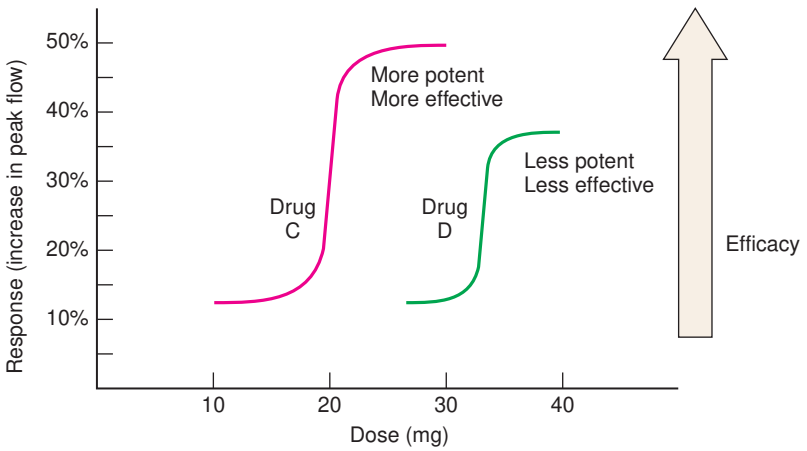
Drug potency refers to the amount of drug required to produce the response desired. When the response is measured against drug concentrations, a dose–response relationship can be seen (please see Figure 1-14). Dose–response

relationships are important for understanding how to titrate drugs to reach maximum efficacy. The lower the dose required to provide a certain effect, the more potent the drug is. Notice in Figure 1-14 that drug A and drug C are more potent (require less of a dose for the desired response) than drugs B and D.

FIGURE 1-14 Dose–Response Curves



Drug A is more potent than drug B.
Drug A is equal to drug B's efficacy or response.



Drug C is more potent than drug D.
Drug C has greater efficacy than drug D.

Efficacy refers to the maximum effect a drug can produce. Unfortunately, the assumption that responses are directly proportional to occupancy at receptors is not valid. The fact that you are occupying a chair in class does not mean that you will learn something. Likewise, the fact that a drug is occupying a receptor does not mean that it will produce a therapeutic effect. Notice in Figure 1-14 that drugs A and B have equal efficacy, whereas drug C has greater efficacy than drug D.

1.8f Tolerance

Clinical pearl

Technically, *tolerance* is the term used for diminished responsiveness that occurs over time and repeated use, whereas *tachyphylaxis* is a more rapidly acquired tolerance after only a few doses.

Patients often ask, "Will this drug lose effectiveness with time?" The relationship between concentration and effect can change over time. Drugs can lose effectiveness because receptors change, are lost, are more readily degraded, or simply adapt. Receptor adaptation can be good and may explain why people become tolerant of side effects of drugs. However, receptor **tolerance** also means that an increased amount of the drug may be needed to produce the same therapeutic effect.

After a cell or tissue has been exposed to a drug for a period of time, it may become less responsive to further stimulation by that agent. This is called **desensitization**. An example of a drug class for which this occurs is the sympathomimetic drugs discussed in Chapter 5. The clinical significance is that desensitization may limit therapeutic response to sympathomimetic drugs when they are needed. Desensitization of beta-receptors to chronic beta-agonist use is a well-known phenomenon that will be discussed in Chapter 5.

Drug **dependence** is a related topic and can be physiologic or psychological. Do you need your coffee in the morning, or do you *need* your coffee in the morning? If patients have withdrawal symptoms when a drug is discontinued, they are dependent. Even laxatives can cause dependence, so that normal bowel movements may not occur after chronic stimulant laxative use.

1.8g Half-Life

Clinical pearl

Smoking can increase the metabolism of theophylline and thus decrease its half-life. Therefore, smokers may need higher theophylline doses than nonsmokers.

Learning Hint

Anything that slows the breakdown of a drug once it is in the body increases its half-life. For example, liver disease increases the half-life of many drugs, because the liver is a major organ for breaking down or metabolizing drugs.

Once a drug is absorbed, attaches to a receptor, and is distributed, it is important to know how long it will remain in the body. Metabolism and excretion are two processes that are responsible for elimination of the drug from the body. By definition, the **half-life** ($T_{½}$) is the amount of time it takes for the concentration of the drug to decrease by half once it is administered. Some drugs have short half-lives and will not stay in the body long. Some drugs have long half-lives and remain in the body for longer periods of time. Dosing frequency may be different for drugs with short or long half-lives, and therefore half-life is also used to determine when a drug administered over time has reached **steady state**, or its maximum concentration in the body.

Steady state means the amount of drug going in is the same as the amount being eliminated. Please again refer back to Figure 1-11. It takes approximately five to six half-lives to reach this steady state. For example if the half-life of a drug is 6 hours, steady state will be reached in 30 to 36 hours. These concepts are also useful in predicting how long it will take for most of the drug to be eliminated from the body. If the patient stops the drug today and it has a half-life of 5 to 6 hours, it will take about 30 to 36 hours (5 to 6 times the drug half-life) for most of the drug to be eliminated from the body. Liver disease may increase the half-life of some drugs that are metabolized by the liver, causing them to stay around longer and have greater-than-expected effects. Table 1-6 lists some common drug half-lives to show the variability that exists.

Table 1-6 **Drug Half-Lives**

Drug	Half-Life
digoxin	30–60 hours
aminoglycosides	2–4 hours
theophylline	7–9 hours
albuterol	2–5 hours
warfarin	0.5–3 days
heparin	1–2 hours

Because it can take a while to reach steady state and the patient may need immediate drug levels for therapeutic effect, a **loading dose** of such drugs as the antibiotic gentamicin or the antiseizure medication phenytoin are frequently used. Loading doses are given at a higher dose than a **maintenance dose** to achieve desired blood concentrations more quickly. Loading doses are used if a patient has not been on a drug before or when the receptors need to be saturated quickly for a quick response. After the initial loading dose is administered, smaller doses (maintenance doses) are needed to maintain adequate therapeutic levels.

1.8h Poisonings/Toxicity

All health-care professionals need to be aware of drug overdoses and poisonings. The study of drugs as they relate to poisonings and environmental toxins is called **toxicology**. It is estimated that there are 2 to 5 million poisonings a year in the United States, with the majority occurring in children younger than 6 years old. Adult poisoning may be intentional or occupational. Because reporting of poisonings is voluntary, the frequency of the problem is unknown.

Poison control centers operate regionally to provide information on poisonings with drugs, chemicals, household products, personal care products, and plants, as well as food poisonings and animal toxins. Information is usually provided on a 24-hour basis and includes management protocols. Childproof medication containers are one way to avoid poisonings.

Emetics (agents that induce vomiting) may be absolutely contraindicated, as in the case of ingestions of caustic agents, so they should not be used until advised by a medical professional. If a product such as a drain cleanser is caustic on ingestion, it can cause even more damage as it is brought back up through the esophagus or aspirated into the lungs. Another treatment of poisoning may include decreasing absorption by giving an adsorbent to bind with the toxic agent and inducing catharsis (bowel movements).

Activated charcoal is used to prevent absorption of some drugs, such as theophylline overdoses. While emesis can remove theophylline from the stomach if induced within 1 hour of ingestion, activated charcoal is effective any time after theophylline exposure. Other drugs have specific antidotes to antagonize the effects of poisoning, for example, *n*-acetylcysteine for acetaminophen (Tylenol®) poisoning and naloxone (Narcan®) for narcotic overdoses presenting as respiratory depression.

Often patients present with respiratory depression when central nervous system (CNS) depressants are taken in overdoses. Toxidromes are signs and symptoms consistent with toxic effects attributed to a particular class of drugs. For example, anticholinergic effects seen in toxicity include increased heart rate, decreased GI motility, pupil dilation, and altered mental status. If a patient presents with those symptoms, then anticholinergic toxicity may be suspected.

Learning Hint

Don't confuse absorption and adsorption. An *adsorbent* binds with a substance to prevent its *absorption*.

1.9 PHARMACOGENOMICS

Pharmacogenomics is a science that examines how genes can explain whether a drug will work or if it will be toxic to our bodies. Enzymes that metabolize drugs are genetically determined. Because of this, some patients may metabolize drugs faster or slower than the average person. This may cause the drug to have a greater effect in a slow or poor metabolizer, and possibly a poor effect—or no effect—in a rapid metabolizer, when compared to the average patient. There are many examples of how pharmacogenomics may help predict drug efficacy or toxicity, but we will provide an example pertinent to respiratory pharmacology.

There is a gene responsible for encoding the beta-2 adrenergic receptor located in the lungs. There are many different variants of this gene in the population. This may explain why some patients are less responsive to beta-2 agonists (bronchodilators) than other patients. The hope is that the science of pharmacogenomics will help optimize drug therapy in individual patients by increasing effectiveness, reducing toxicity, and avoiding unnecessary treatment.

1.10 PRESCRIPTION ORDERS

All drugs require a properly authorized prescription order. Hospitals may have protocols, standing orders, or established therapy guidelines for treating a particular disease. These protocols or guidelines exist to improve the quality of patient care and control costs. Please see Figure 1-15 for the components of a medication order.

FIGURE 1-15 Sample Medication Order.

Note that the DEA# represents the Drug Enforcement Agency number for prescribing controlled substances, as will be further explained in Chapter 11.

Name Jane Cleary Age 36

Address 3376 W. 141st St., Scottsdale Date July 1, 2015

This prescription will be filled generically unless physician signs on line stating "Dispense as written."

℞

Tetracycline 250 mg PO

Disp. #30

Sig. 1 qid take on an empty stomach

Dispense as Written

F. March

Substitution Permissible

Frances March, M.D. 120 Madison Road Scottsdale, NY

DEA # ER639524 Ph. No. 685-9533