# Pharmacology

## *Connections to Nursing Practice*

FIFTH EDITION

Michael Patrick Adams | Carol Quam Urban | Rebecca Sutter

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Dr. Adams obtained his master's degree in pharmacology from Michigan State University and his doctorate in education from the University of South Florida. Dr. Adams was on the faculty of Lansing Community College and St. Petersburg College, and was Dean of Health Professions at Pasco-Hernando State College for over 19 years. He is currently Adjunct Professor of Anatomy and Physiology at Hillsborough Community College.

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

—MPA

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*To my daughter, Joy, an extraordinary nurse who continues to change the world for the better, and in memory of my son, Keith, and my husband, Mike.*

—CQU

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*To my husband, Lee, and my parents, Jane and Ellis, who have given me the foundation to reach for my dreams, and to my amazing children Andrew, Sarah, and Emily, who have made me stronger, better, and more fulfilled than I could have ever imagined. I love you to the moon and back.*

—RES

# Thank You

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We extend a heartfelt thanks to our contributors, who gave their time, effort, and expertise so tirelessly to the development and writing of chapters and resources that helped foster our goal of preparing student nurses for evidence based practice.

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# Preface

Pharmacology is one of the most challenging and dynamic subjects for professional nurses. Each month new drugs are being introduced, and new indications are continually being developed for existing medications. Some medications that were considered preferred drugs only a decade ago are now rarely prescribed. Current knowledge of drug actions, mechanisms, interactions, and legislation is mandatory for nurses to provide safe and effective patient care in all healthcare settings. Pharmacotherapeutics remains a critical and ever-changing component of patient care.

The subtitle of this text, *Connections to Nursing Practice*, has guided its continued development. At a fundamental level, pharmacology is a series of interrelated essential concepts. Some key concepts are shared with the natural and applied sciences. Prediction of drug action requires a thorough knowledge of anatomy, physiology, chemistry, and pathology as well as the social sciences of psychology and sociology. This interdisciplinary nature of pharmacology makes the subject difficult to learn but fascinating to study.

However, the discipline of pharmacology is far more than a collection of isolated facts. To effectively learn this discipline, the student must make connections to nursing practice and, ultimately, connections to patient care. Patients expect to receive effective and safe medication administration from a nurse who is competent in the study of pharmacology. *Pharmacology: Connections to Nursing Practice* identifies key pharmacologic concepts and mechanisms and clearly connects them to current nursing theory and practice for providing optimal patient care.

*Pharmacology: Connections to Nursing Practice* recognizes that pharmacology is not an academic discipline to be learned for its own sake but is a critical tool to prevent disease and promote healing. This connection to patients, their assessment, diagnoses, and interventions supports basic nursing practice. Like other core nursing subjects, the focus of pharmacology must be to teach and promote wellness for patients.

## Structure of the Text

This text is organized according to body systems (units) and diseases (chapters). Unit 1, the first seven chapters, identifies fundamental pharmacologic principles that are applied throughout the text. Although new drugs are constantly being developed, these chapters build the structural framework for understanding the applications of all drugs. The role of complementary and alternative therapies, which are used by many patients, is included in the context of holistic care.

Unit 2 connects pharmacology, the nurse, and the patient, with an emphasis on positive patient outcomes. The four chapters in this unit recognize the essential role of nurse-patient interactions in providing optimal patient care throughout the lifespan. The fact that individuals vary in their responses to drug action is an important theme introduced in this unit.

Units 3 through 11 provide the concepts and connections that are necessary to understand the actions and adverse effects of individual drugs on different body systems. Many of the units begin with a chapter that briefly reviews relevant anatomy and physiology, which is a useful feature for the student when studying drug actions. Each chapter clearly identifies the concepts and connections necessary for safe and effective pharmacotherapy. Pharmacology is intimately related to the study of disease processes. The connections between pharmacology and pathophysiology are clearly established for each drug class in every chapter.

## Resources for Faculty

Pearson is pleased to offer a suite of resources to support teaching and learning, including:

- **TestGen Test Bank**
- **Lecture Note PowerPoints**
- **Instructor's Resource Manual**

# A Practical Approach to Learning Pharmacology



◄ **Disease and Body System Approach.** The organization by body systems (units) and diseases (chapters) places the drugs in context with how they are used therapeutically. This organization connects pharmacology and pathophysiology to nursing care.

► **Prototype Approach.** The vast number of drugs that the practicing nurse must learn is staggering. To facilitate learning, this text uses a prototype approach in which the most representative medications in each classification are introduced in detail. This edition features 194 prototype drugs that include detailed information on therapeutic effects, mechanism of action, pharmacokinetics, adverse effects, contraindications, drug interactions, pregnancy data, and treatment of overdose.

**PROTOTYPE DRUG** **Amiodarone (Nexterone, Pacerone)**

**Classification** **Therapeutic:** Antidysrhythmic, Class III
**Pharmacologic:** Potassium channel blocker

**Therapeutic Effects and Uses:** Approved in 1985, amiodarone is the most frequently prescribed Class III antidysrhythmic. It is considered a broad-spectrum antidysrhythmic because it is effective in terminating both atrial and ventricular dysrhythmias. It is approved for the treatment of resistant ventricular tachycardia and recurrent fibrillation that may prove life-threatening, and it has become a preferred medication for the treatment of atrial dysrhythmias in patients with HF.

**Adverse Effects:** Potentially serious adverse effects limit the use of amiodarone. This drug may cause nausea and vomiting, anorexia, fatigue, dizziness, and hypotension. Visual disturbances are common in patients taking amiodarone for extended periods and include blurred vision due to cornea deposits, photophobia, xerostomia, cataracts, and macular degeneration. Rashes, photosensitivity, and other skin reactions occur in 10 to 15% of patients taking the drug. Certain tissues concentrate this medication; thus, adverse effects may be slow to resolve, persisting long after the drug has been discontinued. **Black Box Warnings:** Amiodarone has been associated with severe and sometimes fatal pulmonary toxicity. It has prodysrhythmic action and may cause bradycardia, cardiogenic shock, or AV block. Liver injury is frequent with amiodarone.

◄ **Updated! Black Box Warnings.** The latest black box warnings issued by the U.S. Food and Drug Administration are clearly identified for all prototype medications. In this edition, black box warnings have been added for non-prototype drugs.

▶ **Updated! Drug Tables.** Every drug table has been revised to add newly-approved drugs and drug classes and remove withdrawn medications. Unique to this text is a listing of the most common and the most serious adverse effects for each drug or drug class. This allows the student to immediately recognize important safety information regarding the drug(s) he or she is administering.

**Table 38.5** Antiplatelet Drugs

| Drug | Route and Adult Dose (Maximum Dose Where Indicated) | Adverse Effects |
|---|---|---|
| anagrelide (Agrylin) | PO: 0.5 mg qid or 1 mg bid (max: 10 mg/day) | *Nausea and vomiting, diarrhea, abdominal pain, dizziness, headache* |
| aspirin (ASA, acetylsalicylic acid) | PO: 80 mg daily to 650 mg bid | |
| dipyridamole (Persantine) | PO: 75–100 mg qid as adjunct to warfarin therapy | Increased bleeding, CNS effects (dipyridamole), anaphylaxis (aspirin), interstitial lung disease (anagrelide) |
| vorapaxar (Zontivity) | PO: 2.08 mg/day | |
| **ADP Receptor Blockers** | | |
| cangrelor (Kengreal) | IV: 30 mcg/kg single dose followed immediately by 4 mcg/kg/minute continuous infusion | *Minor bleeding* Serious bleeding, hypersensitivity, dyspnea |
| clopidogrel (Plavix) | PO: 75 mg/day (max: 300 mg/day for life-threatening cases) | *Minor bleeding, dyspepsia, abdominal pain, headache, rash, diarrhea* Increased clotting time, GI bleeding, blood dyscrasias, angina |
| prasugrel (Effient) | PO: 60-mg loading dose followed by 10 mg/day | |
| ticagrelor (Brilinta) | PO: 180-mg loading dose followed by 90 mg bid | |
| **Glycoprotein IIb/IIIa Receptor Antagonists** | | |
| eptifibatide (Integrilin) | IV: 180 mcg/kg initial bolus over 1–2 min, then 2 mcg/kg/min for 24–72 h (max: 180 mcg/kg bolus, 2 mcg/kg/min infusion) | *Dyspepsia, dizziness, pain at injection site, hypotension, bradycardia, minor bleeding* |
| tirofiban (Aggrastat) | IV: 0.4 mcg/kg/min for 30 min, then 0.1 mcg/kg/min for 12–24 h | Major hemorrhage, thrombocytopenia |
| **Drugs for Intermittent Claudication** | | |
| cilostazol | PO: 100 mg bid | *Dyspepsia, nausea and vomiting, dizziness, myalgia, headache* |
| pentoxifylline (Trental) | PO: 400 mg tid (max: 1200 mg/day) | Tachycardia and palpitations (cilostazol), CNS effects (pentoxifylline), HF, MI |

***Note:*** *Italics* indicate common adverse effects. Underline indicates serious adverse effects.

**Pregnancy:** Animal studies show that lorazepam may cause fetal harm. Neonates born to mothers taking benzodiazepines during pregnancy may experience withdrawal symptoms. Because this drug is secreted in human milk, breastfeeding is not recommended.

◀ **NEW to This Edition:** Pregnancy data for each drug in this text now clearly states known or suspected harm to the embryo or fetus based on laboratory animal and/or human research. Also included is information stating potential harm for the neonate from lactation while the mother is taking the drug. When applicable, this section includes data on recommendations for pregnancy testing prior to and during drug therapy and for the use of contraception while taking the medication.

# Connections to Nursing Practice

"The school nurse recommended we consider Adderall for Jonathon. He's just doing poorly in school and hates to do his homework. Why would he need a drug for that?"
—*Patient "Jonathon Hogan's" mother*

## Chapter 24
## Central Nervous System Stimulants and Drugs for Attention-Deficit/ Hyperactivity Disorder

### Chapter Outline

- Characteristics of Central Nervous System Stimulants
- Etiology and Pathophysiology of Attention-Deficit/ Hyperactivity Disorder
- Pharmacotherapy of Attention-Deficit/ Hyperactivity Disorder
  - Psychostimulants
    - **PROTOTYPE** *Amphetamine and Dextroamphetamine (Adderall, Adderall XR), p. 377*
  - Nonstimulants
    - **PROTOTYPE** *Atomoxetine (Strattera), p. 379*
- Pharmacotherapy of Narcolepsy
  - **PROTOTYPE** *Modafinil (Provigil), p. 381*
- Methylxanthines
  - **PROTOTYPE** *Caffeine (Cafcit), p. 382*

### Learning Outcomes

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

1. Describe the general actions and pharmacotherapeutic applications of central nervous system stimulants.
2. Identify the signs and symptoms of attention-deficit/hyperactivity disorder and narcolepsy.
3. Compare and contrast the central nervous system stimulants and nonstimulants in treating attention-deficit/hyperactivity disorder.
4. Describe the role of stimulant medication in the treatment of narcolepsy.
5. Describe the nurse's role in the pharmacologic management of attention-deficit/hyperactivity disorder and narcolepsy.
6. For each class shown in the chapter outline, identify the prototype and representative drugs and explain the mechanism(s) of drug action, primary indications, contraindications, significant drug interactions, pregnancy data and important adverse effects.
7. Apply clinical judgement to care for patients receiving pharmacotherapy with central nervous system stimulants.

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◀ **Making the Patient Connection** is a feature that opens each chapter with a quote and a photo of a patient. It reinforces to the student that the focus of pharmacology must always be on the patient. To drive this important message home, the patient who is introduced at the start of the chapter is revisited at the end with critical thinking exercises. These questions assist the student to apply the content learned in the chapter to a realistic patient scenario. An additional case study is also included for further application of knowledge learned.

### CASE STUDY: Making the Patient Connection

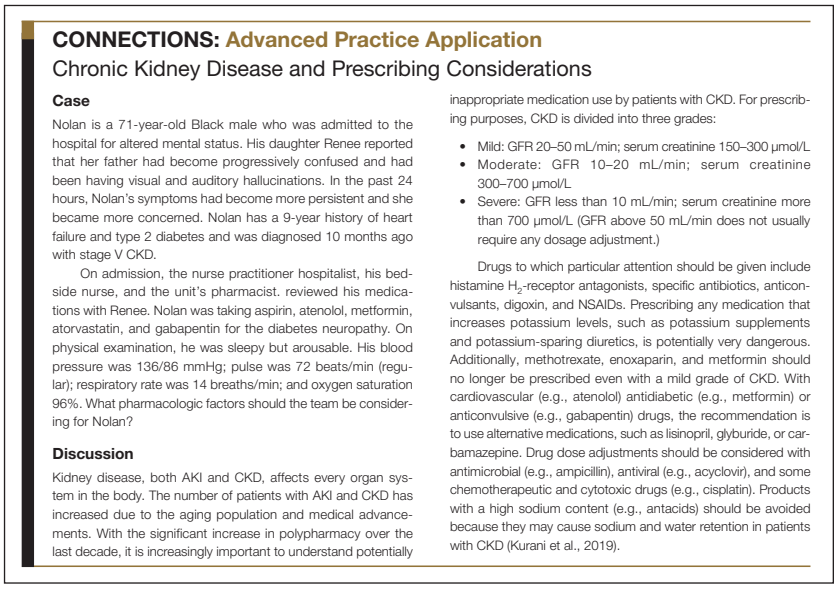
**Remember the patient "Jonathon Hogan" at the beginning of the chapter? Now read the remainder of the case study. Based on the information presented within this chapter, respond to the critical thinking questions that follow.**

Jonathon Hogan has had trouble at school beginning in kindergarten and for the past year. His teachers have consistently reported that he is easily distracted and wanders around the classroom, even during a lesson. Getting him to do his homework after school has been a struggle. Jonathon loves art and does well at video games. Because he is a happy-go-lucky child, his parents have assumed that Jonathon's right-brain dominance has created trouble with left-brain logical work. With more homework now in second grade, Jonathon is struggling to keep up in school. The school nurse suspects he may have ADHD. She has recommended an appointment with Jonathon's healthcare provider and told his parents that Adderall may help him focus on his schoolwork.

#### Critical Thinking Questions

1. What is ADHD and why would Jonathon be experiencing more difficulty as he becomes older?
2. How might amphetamine sulfate and dextroamphetamine (Adderall) help Jonathon with his ADHD?
3. What caregiver education would be appropriate regarding dextroamphetamine and amphetamine sulfate (Adderall)?
4. What are other nonpharmacologic treatments for ADHD?

► **Expanded! Connections: Advanced Practice Applications.** Dramatic changes in the delivery of healthcare have placed an increased emphasis on developing the critical thinking skills and clinical decision-making abilities of nurses at both the undergraduate and graduate levels. Through case studies, the authors use strategies that promote the clinical decision-making skills of advanced practice nurses. Particular attention is paid to advanced practice nurses who are preparing to work within specialty practice settings and with vulnerable populations.



**CONNECTIONS: Advanced Practice Application**

Chronic Kidney Disease and Prescribing Considerations

**Case**

Nolan is a 71-year-old Black male who was admitted to the hospital for altered mental status. His daughter Renee reported that her father had become progressively confused and had been having visual and auditory hallucinations. In the past 24 hours, Nolan's symptoms had become more persistent and she became more concerned. Nolan has a 9-year history of heart failure and type 2 diabetes and was diagnosed 10 months ago with stage V CKD.

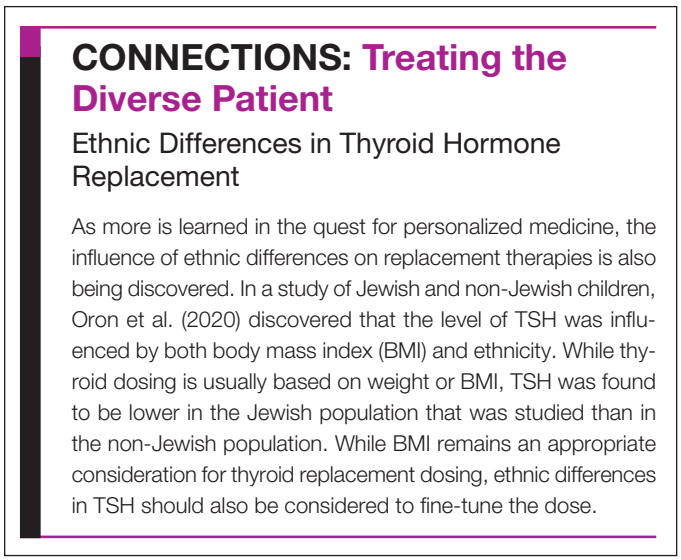
On admission, the nurse practitioner hospitalist, his bedside nurse, and the unit's pharmacist. reviewed his medications with Renee. Nolan was taking aspirin, atenolol, metformin, atorvastatin, and gabapentin for the diabetes neuropathy. On physical examination, he was sleepy but arousable. His blood pressure was 136/86 mmHg; pulse was 72 beats/min (regular); respiratory rate was 14 breaths/min; and oxygen saturation 96%. What pharmacologic factors should the team be considering for Nolan?

**Discussion**

Kidney disease, both AKI and CKD, affects every organ system in the body. The number of patients with AKI and CKD has increased due to the aging population and medical advancements. With the significant increase in polypharmacy over the last decade, it is increasingly important to understand potentially inappropriate medication use by patients with CKD. For prescribing purposes, CKD is divided into three grades:

- Mild: GFR 20–50 mL/min; serum creatinine 150–300 µmol/L
- Moderate: GFR 10–20 mL/min; serum creatinine 300–700 µmol/L
- Severe: GFR less than 10 mL/min; serum creatinine more than 700 µmol/L (GFR above 50 mL/min does not usually require any dosage adjustment.)

Drugs to which particular attention should be given include histamine $H_2$-receptor antagonists, specific antibiotics, anticonvulsants, digoxin, and NSAIDs. Prescribing any medication that increases potassium levels, such as potassium supplements and potassium-sparing diuretics, is potentially very dangerous. Additionally, methotrexate, enoxaparin, and metformin should no longer be prescribed even with a mild grade of CKD. With cardiovascular (e.g., atenolol) antidiabetic (e.g., metformin) or anticonvulsive (e.g., gabapentin) drugs, the recommendation is to use alternative medications, such as lisinopril, glyburide, or carbamazepine. Drug dose adjustments should be considered with antimicrobial (e.g., ampicillin), antiviral (e.g., acyclovir), and some chemotherapeutic and cytotoxic drugs (e.g., cisplatin). Products with a high sodium content (e.g., antacids) should be avoided because they may cause sodium and water retention in patients with CKD (Kurani et al., 2019).



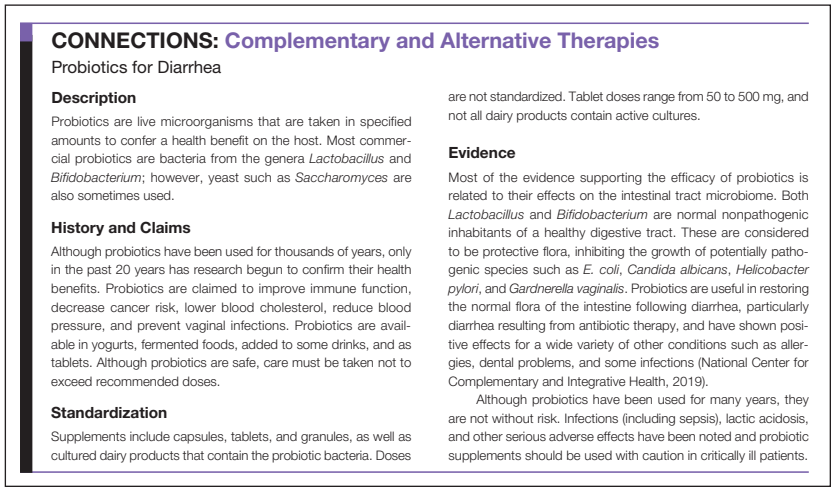
**CONNECTIONS: Treating the Diverse Patient**

Ethnic Differences in Thyroid Hormone Replacement

As more is learned in the quest for personalized medicine, the influence of ethnic differences on replacement therapies is also being discovered. In a study of Jewish and non-Jewish children, Oron et al. (2020) discovered that the level of TSH was influenced by both body mass index (BMI) and ethnicity. While thyroid dosing is usually based on weight or BMI, TSH was found to be lower in the Jewish population that was studied than in the non-Jewish population. While BMI remains an appropriate consideration for thyroid replacement dosing, ethnic differences in TSH should also be considered to fine-tune the dose.

◄ **Connections: Treating the Diverse Patient** features identify gender, cultural, and ethical influences that are important modifiers of drug action.

► **Connections: Complementary and Alternative Therapies** features present herbal therapies and dietary supplements that may be considered as alternatives to conventional drugs. These features include a description of the herb or supplement, history of use, standardization of dose, and brief description of the scientific evidence supporting (or not supporting) the use of the product.



**CONNECTIONS: Complementary and Alternative Therapies**

Probiotics for Diarrhea

**Description**

Probiotics are live microorganisms that are taken in specified amounts to confer a health benefit on the host. Most commercial probiotics are bacteria from the genera *Lactobacillus* and *Bifidobacterium*; however, yeast such as *Saccharomyces* are also sometimes used.

**History and Claims**

Although probiotics have been used for thousands of years, only in the past 20 years has research begun to confirm their health benefits. Probiotics are claimed to improve immune function, decrease cancer risk, lower blood cholesterol, reduce blood pressure, and prevent vaginal infections. Probiotics are available in yogurts, fermented foods, added to some drinks, and as tablets. Although probiotics are safe, care must be taken not to exceed recommended doses.

**Standardization**

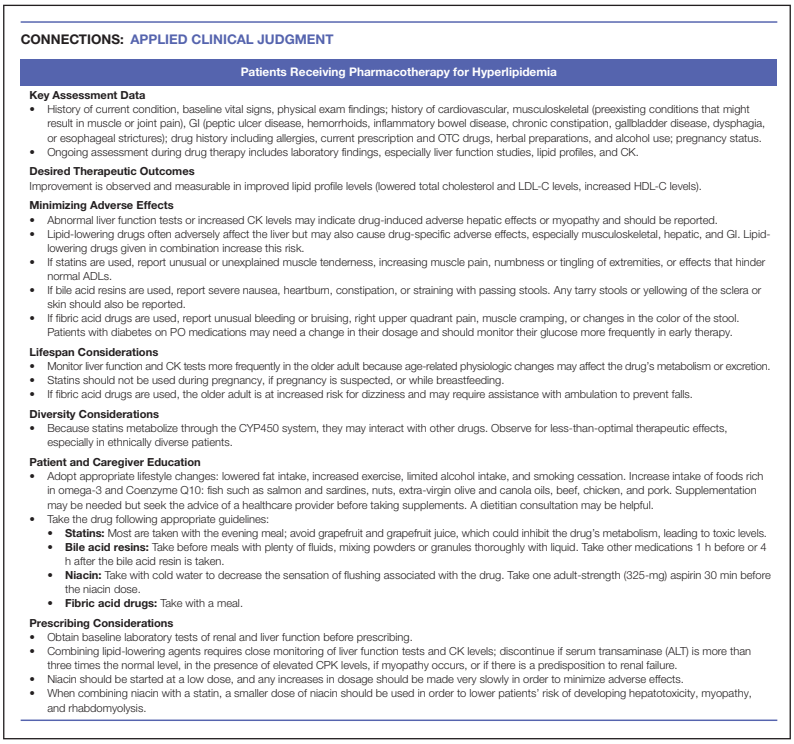
Supplements include capsules, tablets, and granules, as well as cultured dairy products that contain the probiotic bacteria. Doses are not standardized. Tablet doses range from 50 to 500 mg, and not all dairy products contain active cultures.

**Evidence**

Most of the evidence supporting the efficacy of probiotics is related to their effects on the intestinal tract microbiome. Both *Lactobacillus* and *Bifidobacterium* are normal nonpathogenic inhabitants of a healthy digestive tract. These are considered to be protective flora, inhibiting the growth of potentially pathogenic species such as *E. coli*, *Candida albicans*, *Helicobacter pylori*, and *Gardnerella vaginalis*. Probiotics are useful in restoring the normal flora of the intestine following diarrhea, particularly diarrhea resulting from antibiotic therapy, and have shown positive effects for a wide variety of other conditions such as allergies, dental problems, and some infections (National Center for Complementary and Integrative Health, 2019).

Although probiotics have been used for many years, they are not without risk. Infections (including sepsis), lactic acidosis, and other serious adverse effects have been noted and probiotic supplements should be used with caution in critically ill patients.

▶ **Updated! Connections: Applied Clinical Judgment.** Formerly called Nursing Practice Applications, These sections have been totally revised to better reflect the role of the nurse in applying clinical judgment. Based on student feedback, the Applied Clinical Judgment Connections are more concise and in a single column to allow student to rapidly find the essential information they need. Collaboration with other disciplines, such as social support services or dietary services, is also included in the interventions. Important lifespan and diverse patient considerations are noted throughout. The Applied Clinical Judgment features are organized to help students learn to think like a nurse as they take students through the processes of drug administration, nursing care, and teaching that are necessary in pharmacotherapy.



**CONNECTIONS: APPLIED CLINICAL JUDGMENT**

**Patients Receiving Pharmacotherapy for Hyperlipidemia**

**Key Assessment Data**
- History of current condition, baseline vital signs, physical exam findings; history of cardiovascular, musculoskeletal (preexisting conditions that might result in muscle or joint pain), GI (peptic ulcer disease, hemorrhoids, inflammatory bowel disease, chronic constipation, gallbladder disease, dysphagia, or esophageal strictures); drug history including allergies, current prescription and OTC drugs, herbal preparations, and alcohol use; pregnancy status.
- Ongoing assessment during drug therapy includes laboratory findings, especially liver function studies, lipid profiles, and CK.

**Desired Therapeutic Outcomes**

Improvement is observed and measurable in improved lipid profile levels (lowered total cholesterol and LDL-C levels, increased HDL-C levels).

**Minimizing Adverse Effects**
- Abnormal liver function tests or increased CK levels may indicate drug-induced adverse hepatic effects or myopathy and should be reported.
- Lipid-lowering drugs often adversely affect the liver but may also cause drug-specific adverse effects, especially musculoskeletal, hepatic, and GI. Lipid-lowering drugs given in combination increase this risk.
- If statins are used, report unusual or unexplained muscle tenderness, increasing muscle pain, numbness or tingling of extremities, or effects that hinder normal ADLs.
- If bile acid resins are used, report severe nausea, heartburn, constipation, or straining with passing stools. Any tarry stools or yellowing of the sclera or skin should also be reported.
- If fibric acid drugs are used, report unusual bleeding or bruising, right upper quadrant pain, muscle cramping, or changes in the color of the stool. Patients with diabetes on PO medications may need a change in their dosage and should monitor their glucose more frequently in early therapy.

**Lifespan Considerations**
- Monitor liver function and CK tests more frequently in the older adult because age-related physiologic changes may affect the drug's metabolism or excretion.
- Statins should not be used during pregnancy, if pregnancy is suspected, or while breastfeeding.
- If fibric acid drugs are used, the older adult is at increased risk for dizziness and may require assistance with ambulation to prevent falls.

**Diversity Considerations**
- Because statins metabolize through the CYP450 system, they may interact with other drugs. Observe for less-than-optimal therapeutic effects, especially in ethnically diverse patients.

**Patient and Caregiver Education**
- Adopt appropriate lifestyle changes: lowered fat intake, increased exercise, limited alcohol intake, and smoking cessation. Increase intake of foods rich in omega-3 and Coenzyme Q10: fish such as salmon and sardines, nuts, extra-virgin olive and canola oils, beef, chicken, and pork. Supplementation may be needed but seek the advice of a healthcare provider before taking supplements. A dietitian consultation may be helpful.
- Take the drug following appropriate guidelines:
  - **Statins:** Most are taken with the evening meal; avoid grapefruit and grapefruit juice, which could inhibit the drug's metabolism, leading to toxic levels.
  - **Bile acid resins:** Take before meals with plenty of fluids, mixing powders or granules thoroughly with liquid. Take other medications 1 h before or 4 h after the bile acid resin is taken.
  - **Niacin:** Take with cold water to decrease the sensation of flushing associated with the drug. Take one adult-strength (325-mg) aspirin 30 min before the niacin dose.
  - **Fibric acid drugs:** Take with a meal.

**Prescribing Considerations**
- Obtain baseline laboratory tests of renal and liver function before prescribing.
- Combining lipid-lowering agents requires close monitoring of liver function tests and CK levels; discontinue if serum transaminase (ALT) is more than three times the normal level, in the presence of elevated CPK levels, if myopathy occurs, or if there is a predisposition to renal failure.
- Niacin should be started at a low dose, and any increases in dosage should be made very slowly in order to minimize adverse effects.
- When combining niacin with a statin, a smaller dose of niacin should be used in order to lower patients' risk of developing hepatotoxicity, myopathy, and rhabdomyolysis.

## CONNECTIONS: Patient Safety

### Incorrect Insulin Dose

A patient with diabetes has 30 units of Humulin R (regular) insulin ordered for the morning dose. There are several patients with diabetes on the unit and the nurse has given many doses of insulin that morning. The nurse prepares the insulin but draws up Humalog 30 units instead. The patient begins experiencing symptoms of hypoglycemia within 15 minutes and is treated successfully.

What errors occurred and how could they be prevented in the future?

◀ **Connections: Patient Safety,** a QSEN competency, is a feature that presents a brief patient–nurse scenario that illustrates potential pitfalls encountered by nurses that can lead to medication errors. Most scenarios end with a question asking the student to identify what went wrong, what the nurse should do in the situation, what the nurse should question about the order, or what the nurse should do differently in order to prevent medication administration errors.

▶ **Updated! Connections: Using Research in Practice** features illustrate connections to nursing or pharmacology research and discuss the directions of pharmacotherapeutics.

## CONNECTIONS: Using Research in Practice

### Fecal Microbiota Transplant

The role that normal intestinal flora, or *intestinal microbiota*, plays in maintaining body health and immunity is becoming more apparent—and appreciated. Multiple organisms populate the intestinal tract. Their functions include boosting immune protection against toxins produced by some pathogenic bacteria and guarding against septic shock. In addition, they may play a role in preventing obesity.

When normal intestinal flora is disrupted, such as by antibiotic therapy, the pathogenic bacteria may overgrow and cause serious infection. *Clostridioides difficile*–associated diarrhea (CDAD) is a serious bowel infection that most often results from antibiotic therapy. It results in watery diarrhea that contains blood and pus, and rapid dehydration may occur because of fluid loss. The standard treatment for CDAD includes fluid replacement; for severe and recurrent cases, PO vancomycin may be prescribed. Recent research, however, has supported the process called fecal microbiota transplant (FMT), which involves transplanting small amounts of healthy intestinal flora from a donor into a recipient who has CDAD. The outcomes have been positive.

(*continued*)

## CONNECTIONS: Lifespan Considerations

### Miscarriage Prevention with Anticoagulants

Miscarriage in pregnancy is devastating, and recurrent miscarriage even more so. Autoimmune diseases are related to poorer obstetric outcomes than that of the general population, especially in mothers with undiagnosed thrombophilia (genetic hypercoagulability disorders) such as antiphospholipid syndrome. In a study of women who had experienced recurrent miscarriages, after controlling for other potential causes of miscarriage (e.g., metabolic, anatomical, or chromosomal), the prevalence of thrombophilia was found to be higher in women with recurrent miscarriages, compared to the general population (Nahas et al., 2018).

Research on treatment recommendations for the use of heparin, LMWH, or aspirin for recurrent miscarriage before 10 weeks of pregnancy is ongoing and the use of anticoagulant therapy has shown mixed results for prevention of such miscarriages (Lin et al., 2019). It is recommended that a woman experiencing such loss discuss the situation with her provider and whether genetic testing should be conducted. If genetic coagulation abnormalities are found, heparin, LMWH, or aspirin may be considered an option.

◄ **Connections: Lifespan Considerations** features clearly identify important considerations to ensure safe and effective pharmacotherapy in the older adult and pediatric populations.

**CONNECTION Checkpoint 21.3**

The cholinesterase inhibitors for Alzheimer's disease are used for their central actions. From what you learned in Chapter 13, what are the indications for cholinesterase inhibitors that act peripherally? What drug is the prototype peripheral cholinesterase inhibitor?

▲ **Connection Checkpoints** ask the student to recall past concepts from previous chapters that are related to current study. Unique to this text, these reinforce material learned in previous chapters that has direct application to the current chapter.

► **PharmFacts** connect relevant statistics to the presented material. They add interest to the subject and place it in perspective with other nursing concepts.

**PharmFACT**

In 2015 to 2017, 53% of sexually active female teens (age 15 to 19) used oral contraceptives to prevent pregnancy. Emergency contraception in this group was used by 19% (Martinez & Abma, 2020).

▼ **Connections: Community-Oriented Practice** features provide important information that nurses need to convey to their patients to ensure that they receive effective pharmacotherapy after leaving the hospital or clinical setting.

## CONNECTIONS: Community-Oriented Practice

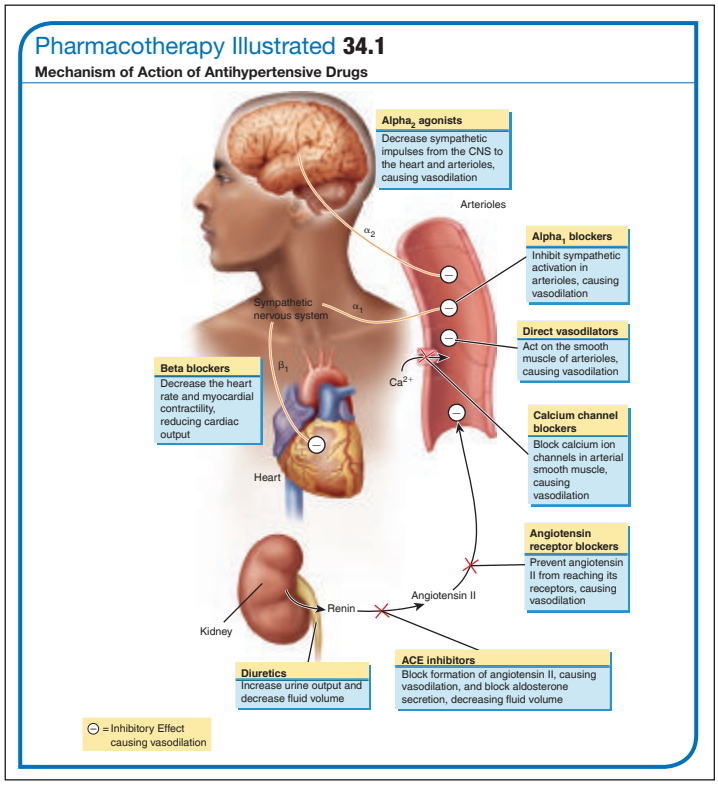
### Lessons Learned from COVID-19 May Aid in TB Control

The response to the pandemic caused by SARS-CoV-2 (COVID-19) overwhelmed the public health communities and shifted attention and resources away from other diseases still very much present and spreading, such as TB. As a leading cause of death, TB remains in the top 10 causes worldwide (WHO, 2020a). Tuberculosis has not disappeared as the COVID-19 pandemic continues and South-East Asia and Africa account for almost 70% of cases worldwide (WHO, 2020b). As testing, tracing, and drug therapies are diverted to COVID-19 and away from TB control, the potential for the spread of the disease, as well as drug-resistant organisms, rises.

But even as the focus of attention moves away from TB and other global diseases to mitigation and management of COVID-19, lessons learned from the response to the pandemic may help to change the way TB is managed and controlled. Social distancing to prevent the spread of TB, contact-tracing measures to determine others in the community who may also need treatment, and the use of modeling to predict disease severity or successful treatment options may be more fully implemented as strategies for TB control. The hope is that communities, public health professionals, and governments can work together and learn from the efforts used for COVID-19 to improve control of other worldwide diseases (Togun et al., 2020).

# Learning Through Visuals

► **Pharmacotherapy Illustrated** features visually present the mechanism of action for many of the prototype drugs, showing students specifically how drugs counteract the effects of disease.



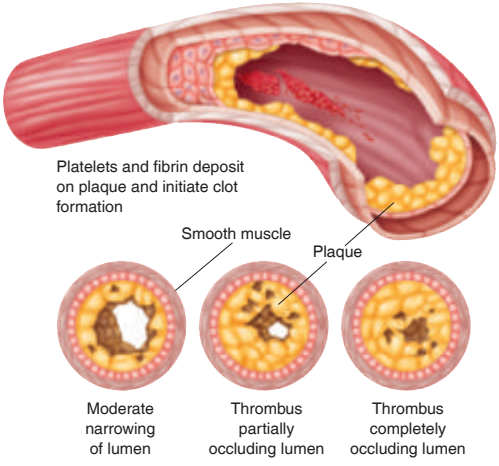




**Figure 35.1** Atherosclerosis in the coronary arteries.

◄ **Vivid, Colorful, and Effective Illustrations** help students review the anatomy, physiology, and pathophysiology of a body system to better understand the impact of disease on that system.

# Understanding the Chapter

The most comprehensive chapter review in its class! **Understanding the Chapter** begins with a **Key Concepts Summary**, which quickly identifies the numbered key concepts from the chapter. Based on student feedback, answers to all the case study and review questions are now included in the text in Appendix A!

► **Making the Patient Connection** reconnects the student to the patient presented in the scenario at the chapter opening. The student learns additional details about the patient's health history and participates in critical thinking questions about the scenario. This allows application of knowledge obtained in the chapter.

## CASE STUDY: Making the Patient Connection

**Remember the patient "Jonathon Hogan" at the beginning of the chapter? Now read the remainder of the case study. Based on the information presented within this chapter, respond to the critical thinking questions that follow.**

Jonathon Hogan has had trouble at school beginning in kindergarten and for the past year. His teachers have consistently reported that he is easily distracted and wanders around the classroom, even during a lesson. Getting him to do his homework after school has been a struggle. Jonathon loves art and does well at video games. Because he is a happy-go-lucky child, his parents have assumed that Jonathon's right-brain dominance has created trouble with left-brain logical work. With more homework now in second grade, Jonathon is struggling to keep up in school. The school nurse suspects he may have ADHD. She has recommended an appointment with Jonathon's healthcare provider and told his parents that Adderall may help him focus on his schoolwork.

### Critical Thinking Questions

1. What is ADHD and why would Jonathon be experiencing more difficulty as he becomes older?
2. How might amphetamine sulfate and dextroamphetamine (Adderall) help Jonathon with his ADHD?
3. What caregiver education would be appropriate regarding dextroamphetamine and amphetamine sulfate (Adderall)?
4. What are other nonpharmacologic treatments for ADHD?

## Additional Case Study

Anna Steinmetz has graduated from nursing school and is working nights. She is having difficulty adjusting to her night schedule. Her healthcare provider suggested she utilize a medication to assist with her adjustment to shift work. She has been prescribed modafinil (Provigil).

1. What effect does modafinil (Provigil) have on the patient's ability to maintain alertness during shift work?
2. What teaching will you provide to the patient regarding this medication?
3. The patient reports feelings of lightheadedness with position changes. What interventions will assist in maintaining patient safety?

◄ An **Additional Case Study** gives students another opportunity to apply their knowledge to patient care.

► **Chapter Review** prepares students for course exams on chapter content.

## Chapter Review

1. An elementary school nurse is providing education to the faculty on the use of central nervous system stimulants to treat attention-deficit/hyperactivity disorder. Of the following, which is most important for the nurse to convey to the faculty?
   1. Have the child bring the drug dose in a lunch bag and come to the office to take it to avoid being teased.
   2. Request that the parents leave an extra copy of the prescription at the school in case the dose runs out.

   better off without me." Which action would the nurse take for this patient?
   1. Tell the patient to stop taking atomoxetine immediately and not to take it until checking with the provider.
   2. Assure the patient that these are normal symptoms because the drug may take 3 or 4 weeks to work.
   3. Alert the family or caregiver that immediate attention and treatment are needed for these symptoms.

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◀ Updated **References** and **Bibliography** provide the foundation for evidence-based nursing practice and support the currency and accuracy of the textbook content.

# New to the Fifth Edition

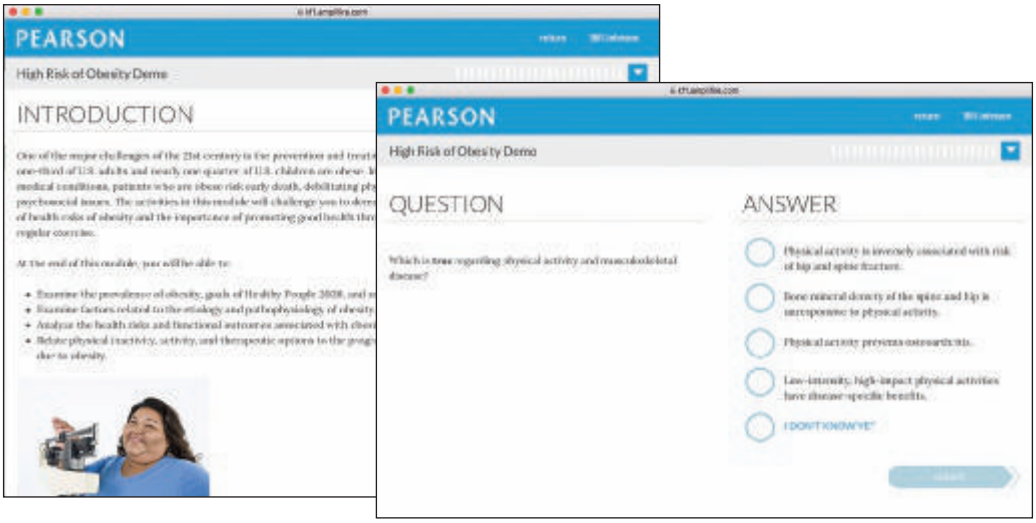
- **New Connection features:** Twenty new Connection features have been added to this edition to reflect changes in nursing practice and pharmacotherapeutics.
- **Updated Connections:** Advanced Practice Application features have been completely revised to help students develop critical thinking and clinical decision-making skills.
- **New Connections:** Applied Clinical Judgment features are now included in most chapters to give students concise instructions on caring for patients taking medications.
- **New:** All answers to case study questions and end of chapter review questions are now included in the textbook so that students can get immediate feedback on key concepts contained within each chapter.
- **Completely Revised:** More than 120 new drugs have been added to update medications approved by the FDA since the previous edition.
- **Current references:** All references have been updated to reflect current nursing practice and pharmacotherapeutics.
- **New:** Pregnancy data for each drug in this text reflects current FDA guidelines. This information includes known or suspected harm to the embryo or fetus based on laboratory animal and/or human research. Also included is information stating potential harm for the neonate from lactation while the mother is taking the drug. When applicable, recommendations are included regarding pregnancy testing prior to and during drug therapy and for the use of contraception while taking the medication.

# MyLab Nursing

MyLab Nursing is an online learning and practice environment that works with the text to help students master key concepts, prepare for the NCLEX-RN exam, and develop clinical reasoning skills. Through a new mobile experience, students can study Pharmacology: Connections to Nursing Practice anytime, anywhere. New adaptive technology with remediation personalizes learning, moving students beyond memorization to true understanding and application of the content. MyLab Nursing contains the following features:

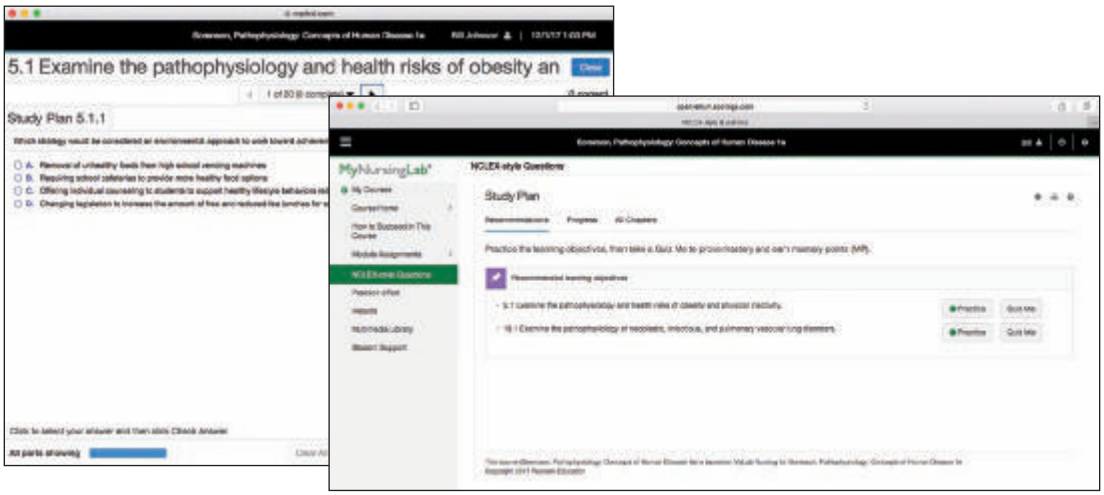
## Dynamic Study Modules

New adaptive learning modules with remediation that personalize the learning experience by allowing students to increase both their confidence and their performance while being assessed in real time.



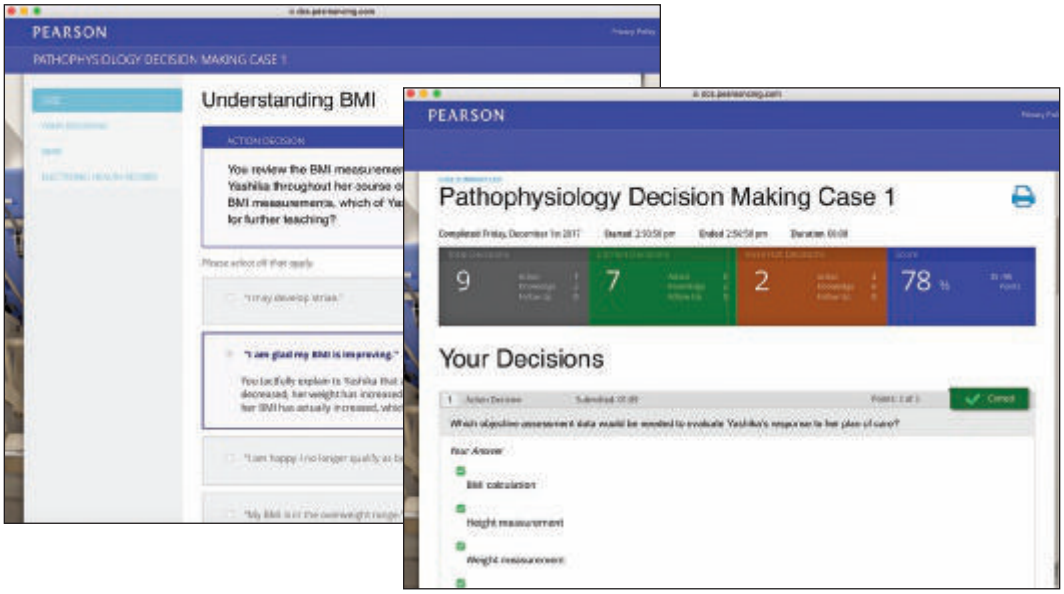

## NCLEX-Style Questions

Practice tests with more than 1000 NCLEX-style questions of various types build student confidence and prepare them for success on the NCLEX-RN exam. Questions are organized by Chapter.



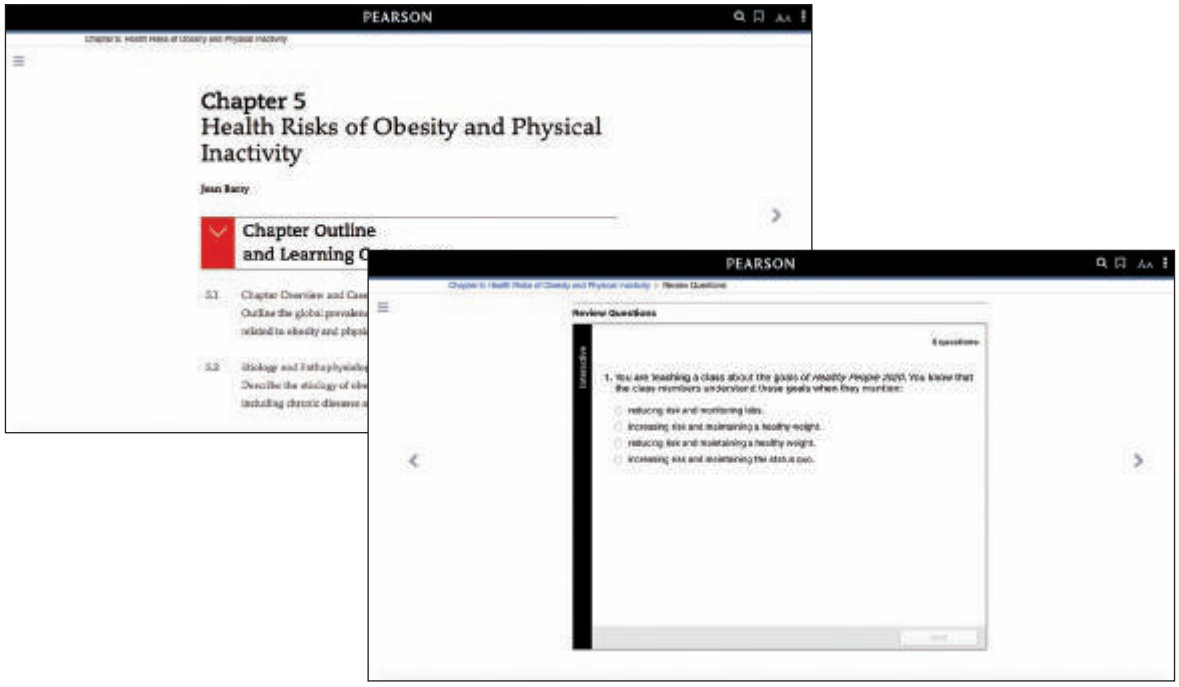
## Decision Making Cases

Clinical case studies that provide opportunities for students to practice analyzing information and making important decisions at key moments in patient care scenarios. These 10 unfolding case studies are designed to help prepare students for clinical practice.




## Pearson eText

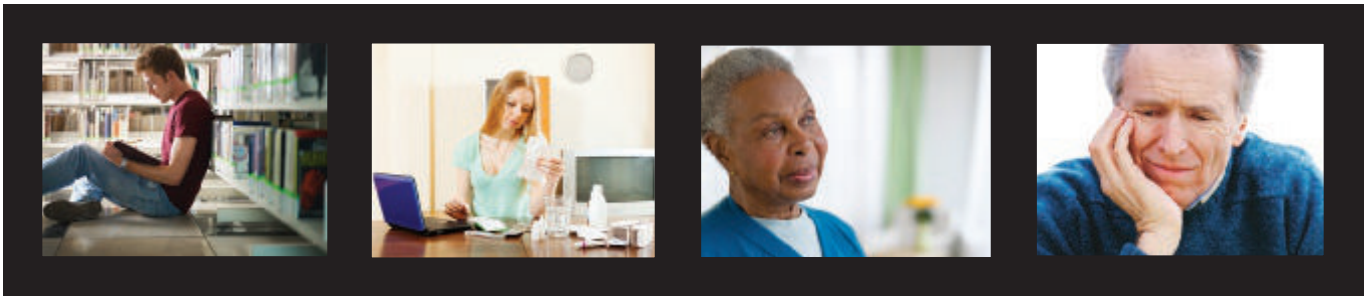
Enhances student learning both in and outside the classroom. Students can take notes, highlight, and bookmark important content, or engage with interactive and rich media to achieve greater conceptual understanding of the text content. Interactive features include audio clips, pop-up definitions, figures, questions and answers, the nursing process, hotspots, and video animations.



# Contents

Unit 1

# Fundamental Principles of Pharmacology



"Wow, I just left my first pharmacology class and my head is swirling. How will I ever remember all this?"
—*Student "Josh Remming"*

# Chapter 1
# Introduction to Pharmacology: Concepts and Connections

## Chapter Outline

- Brief History of Pharmacology
- Pharmacology: The Study of Medicines
- Characteristics of an Ideal Drug
- Classification of Drugs
- Prototype Drugs
- Naming Drugs
- Connecting Pharmacology to Clinical Nursing Practice

## Learning Outcomes

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

1. Identify key events in the history of pharmacology.
2. Compare and contrast the terms *drug*, *pharmacology*, and *pharmacotherapy*.
3. Explain the importance of pharmacotherapy to clinical nursing practice.
4. Using specific examples, explain the difference between the pharmacologic and therapeutic methods of classifying drugs.
5. Identify the advantages of using prototype drugs to study pharmacology.
6. Classify drugs by their chemical, generic, and trade names.
7. Discuss the rationale for a pharmaceutical company receiving exclusivity for the marketing of a new drug.
8. Analyze possible differences between generic drugs and their trade-name equivalents.
9. Identify differences between biosimilar drug, interchangeable drugs and reference product.
10. Identify the responsibilities of the nurse in drug administration as part of an interprofessional team.

## Key Terms

**Definitions of the terms in bold may be found in the Glossary.**

More drugs are being administered to consumers than ever before. Over 5.8 billion prescriptions were dispensed in the United States in 2018, at a rate of more than 17 prescriptions per person (IQVIA Institute, 2019). Sales of prescription medications at retail pharmacies in the United States exceeded $344 billion in 2018. The number and complexity of medications being approved each year bring exciting challenges for nurses and their patients. The purpose of this chapter is to introduce fundamental concepts of pharmacology and to emphasize the connections between drug therapy and clinical nursing practice.

## Brief History of Pharmacology

**1.1 The practice of applying products to relieve suffering has been recorded throughout history by virtually every culture.**

The story of pharmacology is rich and exciting, filled with accidental discoveries and landmark events. Its history likely began when a human first used a plant to relieve symptoms of disease. One of the oldest forms of healthcare, herbal medicine has been practiced in virtually every culture dating to antiquity. The Babylonians recorded the earliest surviving "prescriptions" on clay tablets in 3000 BC, although magic and the art of reading omens were probably considered just as legitimate to healing as the use of herbal remedies. At about the same time, the Chinese recorded the *Pen Tsao* (Great Herbal), a 40-volume compendium of plant remedies dating to 2700 BC. The Egyptians followed in 1500 BC by archiving their remedies on a document known as the Eber's papyrus, which contains over 700 magical formulas and remedies. Galen, the famous Greek physician, described over 1000 healing preparations using plant products before his death in AD 201.

Little is known about pharmacology during the Dark Ages. Although it is likely that herbal medicine continued to be practiced, especially in monasteries and in centers of Arabic culture, few historical events related to drug therapy were recorded. Pharmacology, and indeed medicine, could not advance until the discipline of science was eventually viewed differently than magic and superstition.

The first recorded reference to the word *pharmacology* was found in a text titled "Pharmacologia sen Manuductio and Materiam Medicum" by Samuel Dale in 1693. Before this date, the study of herbal remedies was called "Materia Medica." The term *Materia Medica* likely originated from a Latin term meaning "medical matters," and use of this term continued into the early 20th century.

Although the exact starting date is obscure, modern pharmacology is thought to have begun in the early 1800s. At that time, chemists were making remarkable progress in separating specific substances from complex mixtures. This enabled chemists to isolate the active agents morphine, colchicine, curare, cocaine, and other early drugs from their natural plant products. Pharmacologists could then study their effects in animals more precisely, using standardized amounts. Some of the early researchers even used themselves as test subjects. Friedrich Sertürner, who first isolated morphine from opium in 1805, injected himself and three of his friends with a huge dose of 100 mg of his new product. He and his cohorts experienced acute morphine intoxication for several days afterward.

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

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

The current practice of pharmacology is extremely complex and has progressed far beyond its early, primitive history. The nurses and other health professionals who administer medications, however, must never forget the early roots of pharmacology: the application of products to relieve or prevent human suffering. Whether a substance is extracted from the Pacific yew tree, isolated from a fungus, or created in a laboratory, the central purpose of pharmacology is focused on the patient and improving the quality of life.

**CONNECTION Checkpoint 1.1**

Some modern drugs used in the treatment of diabetes, cardiovascular disorders, and other conditions have unique sources. Using an online dictionary or search engine, what are the natural sources for exenatide (Byetta), captopril (Capoten), and hyaluronic acid? What conditions are they used to treat?

## Pharmacology: The Study of Medicines

**1.2 Pharmacology is the study of medicines.**

The word *drug* has already been used numerous times in this text. What exactly is a drug? Is everything a drug, including water, vitamin C, or perhaps a can of cola? What about substances naturally found in the body, such as estrogen or testosterone? Is it even possible to define a drug?

The definition of a drug is indeed difficult but is nevertheless important to the healthcare profession. There are

many definitions, but perhaps the clearest is that a **drug** is any substance that is taken to prevent, cure, or reduce symptoms of a medical condition. Considering the substances listed earlier, which, then, are drugs? Although it may seem vague, the correct answer is "it depends."

- The caffeine consumed in a cup of coffee is not considered a drug. Yet caffeine is included in several therapies for headache pain, including Excedrin and Fioricet. For the patient trying to get pain relief, caffeine is a drug.
- Vitamin C, if ingested as part of an orange or tomato, is food. Food is not a drug. However, someone with a vitamin C deficiency may be administered vitamin C to cure scurvy. For this patient, vitamin C is then considered a drug.
- A can of cola is certainly not listed in any drug guide. However, if a patient with diabetes is experiencing a hypoglycemic reaction, the glucose in a can of soda may raise the patient's blood sugar and prevent a coma; thus, the glucose in the cola may be considered a drug in this example.
- Substances normally found in the body are not considered drugs unless they are administered to treat a condition. For example, the hormone estrogen circulating in the blood is not a drug. However, when it is taken as an oral contraceptive to prevent pregnancy, estrogen is considered a drug.

Once the meaning of the term *drug* is understood, the next essential term is *pharmacology*. The word *pharmacology* is derived from two Greek words, *pharmakon*, which means "medicine" or "drug," and *logos*, which means "study." Thus, **pharmacology** is most simply defined as the study of medicines. Pharmacology is an expansive subject, ranging from understanding how drugs are administered, to where they travel in the body, to the actual responses they produce. **Pharmacotherapy**, or pharmacotherapeutics, is the application of drugs for the purpose of disease prevention and treatment of suffering.

Drugs are a form of medical intervention given to improve a patient's condition or to prevent harm. Pharmacotherapy often begins when the patient experiences signs or symptoms that cause dissatisfaction with current or future health status. A major role of the nurse is to design interventions that meet the desired health goals of the patient. Pharmacotherapy is a critical intervention for many conditions. The rationale for pharmacotherapy is illustrated in Figure 1.1.

Over 20,000 prescription drugs and combination products are available for pharmacotherapy (U.S. Food and Drug Administration [FDA], 2019) and 40–50 new drugs are approved each year. Each has its own characteristic set of therapeutic applications, interactions, and adverse effects. Many drugs are prescribed for more than one disease and most produce multiple effects on the body. Further complicating the study of pharmacology is the fact that drugs may elicit different responses depending on individual patient factors such as age, gender, race, body mass, health status, and genetics. Indeed, learning the applications of existing medications and staying current with newly approved drugs can be an enormous challenge for the nurse. The task, however, is a critical one for both the patient and the healthcare provider. When applied properly, medications can dramatically improve patients' quality of life. If applied improperly, the consequences of drug action can cause permanent disability and even death.

There are important exceptions to the drug definition mentioned earlier. What about crack cocaine, ecstasy, LSD, or the fumes in glues and paint thinners? These are certainly drugs, but they are not taken "to prevent, cure, or reduce

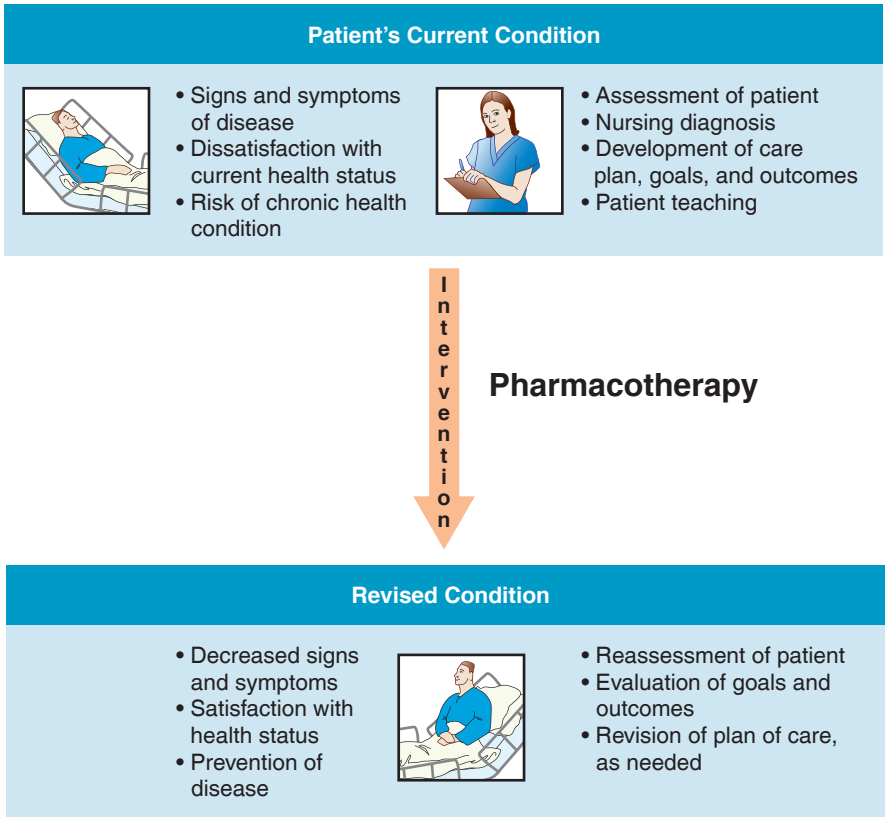



**Figure 1.1** Rationale for pharmacotherapy: A partnership between the patient and the healthcare provider.

Based Centers for Disease Control and Prevention. (2016). Prescription opioid overdose data. Retrieved from http://www.cdc.gov/drugoverdose/data/overdose.html.

symptoms of a medical condition." In fact, they are taken to produce a biologic effect viewed as desirable or pleasurable by the user (see Chapter 27). Other exceptions to this definition of the term *drug* will become apparent as the student studies pharmacology.

## Characteristics of an Ideal Drug

### 1.3 The perfect drug is safe and effective.

As they begin their journey in mastering pharmacology, nursing students should start with a notion of the ideal or "perfect drug." Learning the characteristics of an ideal drug gives a basis for comparison to "real drugs." It is always the goal of pharmacotherapy to select the perfect or ideal drug for the patient. Just what is a perfect drug? It is one that:

- Effectively treats, prevents, or cures the patient's condition.
- Produces a rapid, predictable response at relatively low doses.
- Produces no adverse effects.
- Can be taken conveniently, usually by mouth.
- Can be taken infrequently, usually once a day, and for a short length of time.
- Is inexpensive and easily accessible.
- Is quickly eliminated by the body after it produces its beneficial effect.
- Does not interact with other medications or food.

After reading this description, it should appear clear to the student that there is really no such thing as a perfect drug. Some drugs meet most of the criteria, whereas others meet very few. At the very least, all prescription medications are expected to have some degree of effectiveness at treating or preventing a health condition. The conditions for which a drug is approved are its **indications**. Every medication has at least one indication, and most have multiple indications. Some drugs are used for conditions for which they have not been approved; these are called *unlabeled* or *off-label indications*.

As a general rule, the more a medicine strays from the perfect drug profile, the less commonly it is used. This is because whenever possible, healthcare providers strive to prescribe the most effective, safest, and most convenient medication for the patient. In the home care setting, drugs that cause annoying adverse effects, have inconvenient dosing schedules, or are expensive are often not taken by patients, potentially worsening their condition and causing failure of treatment outcomes. Of course, some essential drugs do produce serious adverse effects or must be given by invasive routes, such as intravenously. In these cases, the drug is either administered in a clinical setting by a nurse or the patient receives careful instructions and regular monitoring on an outpatient basis.

**CONNECTIONS: Patient Safety**

**Preventing Interactions**

A patient has tried to manage symptoms of depression naturally with St. John's wort, an herbal over-the-counter product, without any improvement in symptoms. After over 6 months on St. John's wort he decided to talk to his primary care family nurse practitioner (FNP) about his options. After a thorough assessment, the FNP gives him a prescription for the antidepressant paroxetine (Paxil). It is important for the patient to be educated on any possible interactions. What will this patient need to know about St. John's wort and paroxetine to ensure safe and effective medication therapy? (Refer to this textbook or a drug reference guide for information about paroxetine and potential interactions.)

## Classification of Drugs

### 1.4 Drugs may be organized by their therapeutic classification or pharmacologic classification.

The U.S. Food and Drug Administration (2020a) document *Approved Drug Products with Therapeutic Equivalence Evaluations*, informally called the "Orange Book," lists over 11,000 drugs. With the vast number of drugs available, it is essential that methods be used to group similar agents to aid in their study and understanding. The two basic classifications of drugs are therapeutic and pharmacologic. Both categories are widely used in classifying prescription and nonprescription drugs. The key difference is that the **therapeutic classification** describes what is being treated by the drug, whereas the **pharmacologic classification** describes how the drug acts.

Drugs are placed into therapeutic classes based on their usefulness in treating a specific disease. Table 1.1 shows the method of therapeutic classification, using cardiovascular drugs as an example. Many different types of drugs affect cardiovascular function. Some drugs influence blood coagulation, whereas others lower cholesterol levels or prevent the onset of stroke. Drugs may be used to treat hypertension, heart failure, abnormal cardiac rhythm, chest pain, myocardial infarction (MI), or circulatory shock. Thus,

**Table 1.1** Organizing Drug Information by Therapeutic Classification

**THERAPEUTIC FOCUS: DRUGS AFFECTING CARDIOVASCULAR DISEASE**

| Therapeutic Usefulness | Therapeutic Classification |
|---|---|
| Influence blood clotting | Anticoagulants |
| Lower blood cholesterol | Antihyperlipidemics |
| Lower blood pressure | Antihypertensives |
| Restore normal cardiac rhythm | Antidysrhythmics |
| Treat angina | Antianginals |

drugs that treat cardiovascular disorders may be placed in several therapeutic classes, for example, anticoagulants, antihyperlipidemics, and antihypertensives. The key to therapeutic classification is to simply state what condition is being treated by the particular drug. Other examples of therapeutic classifications include antidepressants, antipsychotics, drugs for erectile dysfunction, and antineoplastics. Notice how the prefix *anti-* often refers to a therapeutic classification.

The pharmacologic classification addresses a drug's mechanism of action or how a drug produces its effect in the body. Table 1.2 illustrates the use of pharmacologic classification, using hypertension as an example. A diuretic treats hypertension by lowering plasma volume. Calcium channel blockers treat this disorder by decreasing the force of cardiac contractions. Other drugs block components of the renin-angiotensin system. Notice that each example describes how hypertension might be controlled. A drug's pharmacologic classification is more specific than its therapeutic classification and requires an understanding of biochemistry and physiology. Pharmacologic classifications may use a drug's chemical name.

Although classifications help to organize drugs, the process is by no means easy or standardized. Most drugs have multiple classifications. For example, the drug epinephrine is classified as a vasoconstrictor, an autonomic nervous system agent, an adrenergic agonist, a sympathomimetic, a bronchodilator, an agent for anaphylaxis, an ocular mydriatic, an antiglaucoma agent, a catecholamine, and a topical hemostatic. This is clearly a mix of therapeutic (e.g., antiglaucoma) and pharmacologic (e.g., catecholamine) classifications. Which one(s) should the student remember? Unfortunately for nursing students, the answer is all of them. The classification chosen primarily depends on the specific clinical use of the drug (What condition is being treated?). Sometimes the classification of choice is simply a preference of the healthcare provider. Although challenging, remembering the different classifications will pay dividends as the student's pharmacology course progresses.

**Table 1.2** Organizing Drug Information by Pharmacologic Classification

**FOCUS ON HOW A DRUG WORKS: PHARMACOTHERAPY OF HYPERTENSION**

| Mechanism of Action | Pharmacologic Classification |
|---|---|
| Lowers plasma volume | Diuretic |
| Blocks heart calcium channels | Calcium channel blocker |
| Blocks hormonal activity | Angiotensin-converting enzyme inhibitor |
| Blocks physiologic reactions to stress | Adrenergic antagonist (or blocker) |
| Dilates peripheral blood vessels | Vasodilator |

**CONNECTION Checkpoint 1.2**

State whether each of the following classifications for aspirin is therapeutic or pharmacologic: anticoagulant, salicylate, central nervous system agent, analgesic, antipyretic. Use a drug guide, if needed.

# Prototype Drugs

## 1.5 A prototype drug is the agent to which all other medications in a class are compared.

As discussed in the previous section, learning thousands of drugs is simplified, at least somewhat, by grouping similar drugs together into broad classifications. Just knowing its therapeutic or pharmacologic classification can reveal important information about a drug. For example, simply knowing whether a drug is used to treat cancer or epilepsy tells you something important about the medication.

An additional strategy is helpful when learning pharmacology. One common and useful practice is to select a single drug from a class and compare all other medications in the class to this representative medication. This is called a **prototype drug**. By learning about the prototype drug in depth, the actions and adverse effects of other drugs in the same class can be predicted. For example, by learning the actions and effects of penicillin V, students can extend this knowledge to all other drugs in the penicillin class of antibiotics. In this textbook, the drug prototypes are clearly identified, and detailed information regarding their therapeutic effects, mechanism of action, adverse effects, contraindications, precautions, and nursing responsibilities, including patient and family education, is presented.

Selecting a drug to serve as the prototype for a class is not always a simple matter; healthcare providers and textbooks sometimes disagree. The traditional prototype approach uses the oldest and best understood drug in the class. For example, atropine has been used for thousands of years and still remains a prototype drug for certain indications (see Figure 1.2). Sometimes, however, newer drugs are


**Figure 1.2** Obtained from the deadly nightshade plant *Atropa belladonna*, atropine remains a traditional prototype drug.
Heike Falkenberg/Fotolia.

developed in the same class that are more effective or have a more favorable safety profile. Over time, an older prototype drug may be infrequently prescribed and a different, more clinically useful prototype may be chosen for the class. This textbook uses a practical approach to prototype drugs, selecting a combination of traditional drugs and those most widely used. Regardless of the approach, the student must remember that the prototype is the drug to which all others in a class are compared.

# Naming Drugs

## 1.6 Drugs have chemical, generic, and trade names.

Despite the utility of using drug classes and prototypes when studying pharmacology, learning thousands of drug names remains a challenge. Adding to this difficulty is that most drugs have multiple names. The three basic types of drug names are chemical, generic, and trade names.

**Chemical names** are assigned using standard nomenclature established by the International Union of Pure and Applied Chemistry (IUPAC). A drug has only one chemical name. This chemical name is sometimes helpful in predicting a drug's physical and chemical properties. Although chemical names convey a clear and concise meaning about the nature of a drug to the chemist, these names are often complicated and difficult to remember or pronounce. For example, it is unlikely that the nurse would remember that the chemical name for alprazolam (Xanax) is 8-chloro-1-methyl-6-phenyl-4H-s-triazolo[4,3-α][1,4]-benzodiazepine. In only a few cases, usually when the name is brief and easily remembered, will nurses use chemical names. Examples of easy-to-remember chemical names of common drugs include lithium carbonate, calcium gluconate, and sodium chloride.

Drugs are sometimes named and classified by a *portion* of their chemical structure, known as the chemical group name. In the Xanax example, a portion of the chemical name, benzodiazepine, is used as a drug class. Other examples include the fluoroquinolones, aminoglycosides, phenothiazines, and thiazides. Although these names may seem complicated when first encountered, knowledge of chemical group names will become invaluable as the nursing student begins to learn and understand the actions of the drugs in the major drug classes.

The **generic name** of a drug is assigned by the United States Adopted Names Council. With few exceptions, generic names are less complicated and easier to remember than chemical names. Many organizations, including the FDA, the United States Pharmacopeial Convention, and the World Health Organization, routinely describe a medication by its generic name. Because each drug has only one generic name, healthcare providers often use this name, and students must memorize it. Fortunately, sometimes components of a generic name can help a student recognize other drugs in that same class. For example, the ending *-lol* is used in the generic name of beta-adrenergic blockers, and the ending *-statin* denotes a lipid-lowering drug.

A drug's **trade name**, sometimes called the *proprietary*, *product*, or *brand name*, is assigned by the pharmaceutical company marketing the drug. The trade name is intentionally selected to be short and easy to remember so that patients will remember it and ask for it by name. The term *proprietary* suggests ownership. Indeed, many times a manufacturer holds a legal patent on the drug.

Trade names are a challenge for students to learn because there may be dozens of products that contain the same drug. For example, if the nurse is looking for aspirin, it may be listed under many trade names, including Acuprin, Aggrenox, Anacin, Aspergum, Bayer, Bufferin, Durlaza, Ecotrin, Excedrin Migraine, Fiorinal, Lanorinal, Percodan, Salocol, Vanquish, Vazalore, and Zorprin, formulated alone or in combination with other active ingredients. Acetaminophen is an additional example of a drug that appears in multiple combination products with dozens of different trade names. Further complicating the naming of proprietary drugs is that trade names change very frequently. To avoid this confusion, generic names should be used when naming the active ingredients in a combination product. When referring to a drug, it is conventional to write the generic name in lowercase first, followed by the trade name in parentheses with the first letter capitalized. Examples include alprazolam (Xanax) and acetaminophen (Tylenol).

Drugs with two or more active generic ingredients are called **combination products**. These products are usually formulated into a single tablet, capsule, solution, prefilled syringe, or inhaler. It is more convenient for the patient to take a single combination product rather than two or more different medications separately. Combination products are especially common in over-the-counter cold remedies, antihypertensives, vaccines, and therapies for HIV infection.

## 1.7 Generic drugs are less expensive than trade-name drugs, but they may differ in bioavailability.

In the United States, the pharmaceutical company marketing the medication determines the price of a medication. When a drug is newly marketed, there is no competition and the price can be very high. Once competing companies begin to market the generic equivalent drug, consumer savings may be substantial. In many states, pharmacists may routinely substitute a generic drug when the prescription calls for a trade name, a practice called **pharmacy-level substitution**. In other states, the pharmacist must dispense drugs directly as written by a healthcare provider or obtain approval before providing a generic substitute.

Are there significant differences in quality between a trade-name drug and its generic equivalent? The key to comparing trade-name drugs and their generic equivalents lies in measuring the **bioavailability** of the two agents. Bioavailability is defined by the Food, Drug, and Cosmetic Act (see Chapter 2) as the rate and extent to which the active ingredient is absorbed from a drug product and becomes available at the site of drug action to produce its effect. Bioavailability is affected by many factors, including inert ingredients and tablet compression. Anything that affects the absorption of a drug or its travel to its target cells can certainly affect drug action. Measuring how long a drug takes to exert its effect (onset time) gives pharmacologists a crude measure of bioavailability. If the trade and generic products have the same rate of absorption and have the same onset of therapeutic action, they are said to be *bioequivalent*.

The importance of bioavailability differences between a trade-name drug and its generic equivalent depends on the specific circumstances of pharmacotherapy. For example, if a patient is in circulatory shock and the generic equivalent drug takes 5 minutes longer to produce its effect, that may indeed be significant. However, if a generic medication for arthritis pain relief takes 45 minutes to act, compared to 40 minutes for the trade-name drug, it probably does not matter which drug is used, and the inexpensive product should be prescribed to provide cost savings to the consumer. As a general rule, bioavailability is of most concern when using critical-care drugs and those with a narrow safety margin. In these cases, the patient should continue taking the trade-name drug and *not* switch to a generic equivalent, unless approved by the healthcare provider. For most other drugs, the generic equivalent may be safely substituted for the trade-name drug.

In the age of internet pharmacies, the issue of marketing rights has drastically changed. Other countries are not bound by U.S. drug laws, and patients sometimes obtain medications through the mail at a fraction of the cost in the United States. For example, a pharmaceutical company may have the exclusive rights to sell Cialis in the United States, but companies in India and China are able sell the identical drug through internet pharmacies and ship it to customers in the United States. In some cases, they may sell the drug to consumers without a prescription. Some countries do not have the same high-quality manufacturing standards as the United States, and the patient may be purchasing a useless or even harmful product. Furthermore, although some internet sites may appear to be based in the United States, they may instead be obtaining their medications from sources outside the United States. Nurses must urge their patients not to purchase drugs from overseas pharmacies because there is no assurance that the drugs are safe or effective.

**PharmFACT**

Nine out of every 10 prescriptions dispensed in the United States are for generic drugs, and 95% of these costs $20 or less (Association for Accessible Medicines, 2020).

## 1.8 Biologic products are drugs produced from living cells.

**Biologic products (BPs)** are substances made by living cells obtained from humans, animals, plants, or microorganisms. These include a diverse range of products produced through biotechnology, gene therapy and tissue research. Because of their natural origin, BPs are often complex mixtures in which individual chemical structures cannot be easily identified or characterized. In recent years, some BPs have become cutting-edge treatments for rheumatoid arthritis, multiple sclerosis, and cancer. Although effective medications, they are usually very expensive. For example, some of the newer BPs for cancer cost thousands of dollars per dose.

Several laws have been passed in an attempt to increase the availability of biologics and lower their costs. These laws created two new categories: biosimilar BPs and interchangeable BPs.

As defined by the FDA (2020b), "A **biosimilar drug** is a biological product that is highly similar to and has no clinically meaningful differences from an existing FDA-approved reference product." The **reference product** is the original BP that underwent rigorous testing and was approved by the FDA based on a thorough evaluation of its safety and effectiveness.

Is a biosimilar drug the same thing as a generic drug? Recall that a generic drug is an identical chemical copy of the brand-name drug. Because a biosimilar is *not* an exact, duplicate copy of the original medication (reference product), it is not called a generic medication. Biosimilars are not required to undergo the same rigorous preclinical and clinical testing as their reference products; therefore, they are less expensive to bring to market. To be approved as a biosimilar, however, the manufacturer must demonstrate to the FDA that the drug differs very little from the approved reference product. The biosimilar must have the same route of administration, dosage forms, mechanism of action, and clinical indications as the reference product. The first biosimilar, Zarxio, was approved by the FDA with the same indications as filgrastim (Neupogen), the reference product. More than 26 biosimilars have since been approved, and dozens are in the approval process. The FDA gathers information on BPs in the "Purple Book." This is actually not a book at all but an online list of licensed biological products with reference products and biosimilars (FDA, 2020c).

The FDA created an additional category for BPs called **interchangeable products**. An interchangeable product is a biosimilar that has undergone a higher standard of *additional*

testing. This testing must show that the interchangeable product produces the same clinical result as the reference product in any given patient. If the product is to be administered more than once, the manufacturer must show that the safety and effectiveness is not changed if the interchangeable product is switched back and forth with the reference product.

Why would a manufacturer provide additional time-consuming (and expensive) testing to the FDA so its product can be classified as an interchangeable product instead of a biosimilar? The answer lies at the pharmacy counter. Recall that in most states, when a practitioner writes a prescription for a trade-name drug, the pharmacist has the authority to substitute a generic medication. However, if a practitioner writes a prescription for a BP that is a reference product, the pharmacist *cannot* substitute a biosimilar. The pharmacist, however, *can* substitute an interchangeable product for the reference product. Of course, laws on pharmacy-level substitution differ among states and the topic of pharmacy-level substitution of biosimilars is rapidly evolving.

The naming of biological products and biosimilars is different than other drugs. When a new biosimilar is approved by the FDA, it receives a product name followed by a hyphen and a four-letter suffix. For example, adalimumab (Humira) was approved in 2002 and is a reference drug. The following are approved biosimilars:

adalimumab-atto (Amjevita) approved in 2016
adalimumab-adbm (Cyltezo) approved in 2017
adalimumab-adaz (Hyrimoz) approved in 2018
adalimumab-afzb (Abrilada) and adalimumab-bwwb (Hadlima) approved in 2019

The four-letter suffix does not denote any property of the BP; in fact, it is purposely meant to be devoid of meaning. It is assigned to track each specific biosimilar, in the event unusual adverse events occur or other differences between products appear during clinical use.

In 2019, adalimumab was the best-selling drug in the world and the retail cost for 26 injector pens (1 year's medication) was over $120,000 in the United States. Will the existence of biosimilars affect the cost of therapy with adalimumab? The answer is unknown in the United States because patent lawsuits have kept all five adalimumab biosimilars from reaching the market. The United Kingdom and Scandinavian countries, however, have experienced a 70–80% drop in cost due to biosimilar use.

# Connecting Pharmacology to Clinical Nursing Practice

## 1.9 Effective pharmacotherapy depends on a thorough understanding of pharmacology.

Pharmacotherapy has become a mainstay of modern medical treatment, and a thorough understanding of expected drug effects, the associated monitoring required, and the care and teaching associated with drugs that are prescribed in patient care is crucial to effective practice. As a member of an interprofessional team, nurses, physicians, advanced practice nurses, pharmacists, and, most importantly, the patient work together to achieve optimal therapeutic outcomes from drug therapy. The importance of pharmacology to clinical practice cannot be overstated and will be emphasized throughout this textbook.

One major goal of this text is to provide a solid foundation in the knowledge of pharmacology and pharmacotherapeutics. Chapters 2 through 4 provide the legal and scientific bases for pharmacotherapeutics. As a member of an interprofessional healthcare team, it is most often the nurse who serves as the connection between a prescription and the patient's safe use of the prescribed drug. Monitoring the patient's condition before and during drug use, evaluating drug effects, teaching the patient about self-administration, and conducting a medication reconciliation are key nursing responsibilities. For the advanced practice nurse, an understanding of the pathophysiology underlying the patient's current condition, excellent assessment skills, and clinical decision-making skills aimed at choosing the best treatment options are required.

A major goal in studying pharmacology is to eliminate medication errors and to limit the number and severity of adverse drug events. Many adverse effects are preventable. We, as healthcare providers, can routinely avoid many serious adverse drug effects in patients by applying experience and knowledge of pharmacotherapeutics to clinical practice. Unfortunately, though, some adverse effects are simply not preventable. It is critical that the entire interprofessional team be prepared to recognize and respond to potential adverse effects of medications. The management of adverse effects and medication errors are discussed in Chapters 5 and 6, respectively.

Before any drug is administered, it is important to ask about pertinent information regarding the patient's medical history, complete a thorough physical assessment, and assess learning needs and capabilities. Growth and developmental factors must always be considered. It is important to remember that a large number of variables influence a patient's response to drugs throughout the lifespan. Having a firm understanding of these variables can increase treatment success. Chapters 8 through 11 of this textbook address these aspects of pharmacotherapy.

Knowledge of pharmacology is an ongoing, lifelong process that builds with clinical practice and chooses of specific clinical areas. Early in practice, learning prototype drugs that represent a specific classification of drugs, recognizing key similarities in generic names, and always looking up unknown or new drugs will help build this knowledge base. As experience grows, anticipating drug effects and care and teaching needs becomes integrated

into practice. For an advanced practice nurse working as a nurse practitioner, this clinical experience helps to enhance the new information acquired to prepare for prescriptive authority. Chapters 12 through 75 present the foundational knowledge needed for effective pharmacotherapy. Each unit begins with a review of the anatomy and physiology underlying the mechanism of action of drugs discussed in the unit, followed by detailed information about specific classifications of drugs and nursing responsibilities for those classifications.

Despite its essential nature, the study of pharmacology should be viewed in the proper perspective. Although pharmacology is a key intervention in many cases, all healthcare providers must use all the healing sciences in treating their patients. The effectiveness of a drug in treating disease can never substitute for skilled, compassionate care. Too much reliance on drug therapy can diminish the importance of the nurse–patient relationship.

# Understanding Chapter 1

## Key Concepts Summary

**1.1** The practice of applying products to relieve suffering has been recorded throughout history by virtually every culture.

**1.2** Pharmacology is the study of medicines.

**1.3** The perfect drug is safe and effective.

**1.4** Drugs may be organized by their therapeutic classification or pharmacologic classification.

**1.5** A prototype drug is the agent to which all other medications in a class are compared.

**1.6** Drugs have chemical, generic, and trade names.

**1.7** Generic drugs are less expensive than trade-name drugs, but they may differ in bioavailability.

**1.8** Biologic products are drugs produced from living cells.

**1.9** Effective pharmacotherapy depends on a thorough understanding of pharmacology.

## CASE STUDY: Making the Patient Connection

**Remember the student "Josh Remming" at the beginning of the chapter? Now read the remainder of the case study. Based on the information presented within this chapter, respond to the critical thinking questions that follow.**

Josh Remming, a 23-year-old student, is in his first semester of nursing school. He thought that nursing would provide him with a great career and lots of opportunity. He enjoys helping people and has always been fascinated with healthcare. However, after the first pharmacology class, Josh is worried because there seems to be an overwhelming amount of content to learn in just one semester.

At the end of the class, Josh talks with other students who are concerned and a bit anxious. Much of the conversation centers around lecture content provided by the professor. Following are some of the questions from Josh's classmates. How would you respond?

### Critical Thinking Questions

1. What is the difference between therapeutic classification and pharmacologic classification?
2. What classification is a barbiturate? Macrolide? Birth control pills? Laxatives? Folic acid antagonist? Antianginal agent?
3. What is a prototype drug, and what advantages does a prototype approach to studying pharmacology offer?
4. Why do nurses need to know all this pharmacology?

## Additional Case Study

Sarah Hawkins, an older woman who lives on a fixed income, is on multiple medications. She says that all her friends are taking the generic form of their medications. During her appointment, she asks, "What do you think of generic medicines? Are they safe? Are they as good? Are they worth it?"

1. How do generic equivalent drugs differ from a proprietary (trade-name) drug?
2. What would you recommend that Sarah do about accepting generic drugs?

## Chapter Review

1. While using a drug handbook to determine the indications for the drug furosemide (Lasix). The term *indications* is defined as the:
    1. Way a drug works on the target organs.
    2. Amount of the drug to be administered.
    3. Conditions for which a drug is approved.
    4. Reason that the drug should not be given.

2. In reviewing the patient's medication record, the nurse does not recognize the medication, filgrastim-sndz (Zarxio). Consulting a drug guide, it is listed as a "biosimilar" to filgrastim (Neupogen). Which of the following best describes the definition of a biosimilar drug?
    1. It is another term for a "generic" drug when the two drugs exert similar biologic effects.
    2. It is a drug that has similar effects on the body but belongs in a different chemical and therapeutic classification.
    3. It is a drug that is derived from living cells, such as yeast, and has comparable effectiveness and safety to the reference product drug.
    4. It is a drug that is identical to the reference product drug and thus does not require FDA approval.

3. As a member of an interprofessional team, what key responsibilities does the nurse have to ensure effective pharmacotherapy? (Select all that apply.)
    1. Monitoring the patient's condition before and during pharmacotherapy
    2. Teaching the patient about self-administration and any required monitoring of drug effects
    3. Ensuring that all drug and treatment options have been considered before beginning pharmacotherapy
    4. Frequently conducting a medication reconciliation to verify current medications in use
    5. Determining the ideal drug to be prescribed to the patient to treat the current condition

4. Which patient characteristics, if noted in the patient's medical record, should you consider important information that may affect the physiologic response to various types of drug therapy? (Select all that apply.)
    1. 82-year-old and female
    2. Asian and obese
    3. Past medical history of kidney disease
    4. Mother and sister with diabetes
    5. Has no medical insurance

5. Which of the following would indicate a therapeutic classification?
    1. Beta-adrenergic antagonist
    2. Antihypertensive
    3. Diuretic
    4. Calcium channel blocker

6. Why would a manufacturer provide additional time-consuming (and expensive) testing to the FDA so its product could be classified as an interchangeable product instead of a biosimilar?
    1. So the pharmacist could substitute a generic medication.
    2. So that the pharmacist could substitute a biosimilar product for the reference product.
    3. Because federal laws dictate a pharmacy-level substitution for a biosimilar.
    4. Biosimilars are exact, duplicate copies of the original medication and therefore are interchangeable, so additional testing wouldn't be needed.

*See Appendix A for answers to critical thinking questions, case study questions and review questions.*

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"This headache medicine I bought at the grocery store must be safe because I didn't need a prescription."
—*Patient "Gertrude Stone"*

# Chapter 2
# Drug Regulations

## Chapter Outline

- Patent Medicines
- Brief History of Drug Legislation
- Drug Standards
- The U.S. Food and Drug Administration
- Drug Approval
- Changes to the Drug Approval Process
- Prescription and Over-the-Counter Drugs
- Drug Schedules
- Prescriptive Authority for Nurses

## Learning Outcomes

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

1. Explain the role of patent medicines in the history of pharmacology and the legislation of drugs.
2. Outline the key U.S. drug regulations and explain how each has contributed to the safety and effectiveness of medications.
3. Describe how the *United States Pharmacopeia-National Formulary* (USP-NF) controls drug purity and standards.
4. Evaluate the role of the U.S. Food and Drug Administration in the drug approval process.
5. Categorize the four stages of new drug approval.
6. Explain the role of a placebo in new drug testing.
7. Discuss how changes to the approval process have increased the speed at which new drugs reach consumers.
8. Compare and contrast prescription and over-the-counter drugs.
9. Explain how scheduled drugs are classified and regulated.
10. Explain how advanced practice nurses are helping to fill the primary care workforce gap.

## Key Terms

**Definitions of the terms in bold may be found in the Glossary.**

Laws govern all aspects of the drug approval, labeling, marketing, manufacturing, and distribution process. The primary purpose of this legislation is to protect the public from unsafe and ineffective products. This chapter examines standards and legislation regulating drugs in the United States.

# Patent Medicines

## 2.1 Early American history saw the rise of patent medicines and the lack of adequate drug regulations.

People have an expectation that the medication they are taking is effective at treating their condition, whether it is asthma, diabetes, or a headache. They expect the label to contain clear and accurate instructions on how the product should be taken. They expect that the drug will be safe when the instructions are correctly followed. Are these reasonable assumptions? In the United States and Canada, the answer is yes. But Americans have not always had this reassurance. Although drugs have been used for thousands of years, it was not until the 20th century that extensive standards and regulations were developed to protect the public from unsafe and ineffective products.

In early America, there were few attempts to regulate drugs. This period saw the rise of **patent medicines**. Although the term *patent* implies a legal right to manufacture or sell a drug, this was not the case. Patent medicines contained a trade name that clearly identified the product, such as William Radam's Microbe Killer, Stanley's Snake Oil, Dr. Kilmer's Swamp Root, or Dr. Moore's Indian Root Pills. Because there were no laws to the contrary, these products went untested and could claim to cure nearly any symptom or disease. Dr. William's Pink Pills for Pale People, which contained iron oxide and magnesium sulfate, claimed to cure rheumatism, nervous headache, palpitations, grippe, neuralgia, locomotor ataxia, partial paralysis, sallow complexion, and all forms of weakness in men or women. A typical advertisement from this era is shown in Figure 2.1.


**Figure 2.1** Patent medicines contained a trade name that clearly identified the product and claimed to cure just about any symptom or disease.
Library of Congress Prints and Photographs Division Washington [LC-USZC4-1032].

Patent medicines were often harmless (and ineffective), containing coloring, flavoring, and an aromatic substance that "smelled like medicine." At their worst, some contained hazardous levels of dangerous or addictive substances. In fact, cocaine, heroin, and morphine were freely distributed in patent medicines; some elixirs contained up to 50% morphine, which indeed caused many painful disorders to "disappear." Addictive ingredients were purposely added to guarantee repeat customers for their products. (Note the similarity with nicotine added to tobacco and caffeine added to soft drinks.) In the late 1800s, the familiar Coca-Cola soft drink was a patented beverage that contained an estimated 9 mg of cocaine per serving and was claimed to cure headache, dyspepsia, hysteria, morphine addiction, and impotence. The need for stricter regulation became more apparent in the 1860s as cocaine was synthesized, and the use of opiates as painkillers during the Civil War caused thousands of soldiers to become addicted.

Although the marketing and use of patent medicines may seem humorous and even unbelievable to modern consumers, a few of these products are still available over the counter (OTC). Examples of patent medicines that survived the drug regulations of the 1900s include Smith Brothers Throat Drops, Fletcher's Castoria, Doan's Pills, Vick's VapoRub, and Phillip's Milk of Magnesia. Of course, the ingredients of these products have changed over time so that they conform to modern regulations regarding labeling, safety, and effectiveness.

# Brief History of Drug Legislation

## 2.2 In the 1900s, drug legislation was enacted to make drugs safer and more effective.

Although individual states attempted to regulate drugs, the first national law was the Drug Importation Act, passed in 1848, which attempted to stop the entry of unsafe drugs into the United States. In the early 1900s, the United States began to develop and enforce tougher drug legislation to protect the public. This was spurred, in part, by the tragic deaths of 13 children in St. Louis in 1901 who were given diphtheria antitoxin that was contaminated with tetanus. In 1902, the Biologics Control Act was passed to standardize the quality of sera, antitoxins, and other blood-related products. Passed shortly thereafter, the Pure Food and Drug Act (PFDA) of 1906 was a significant and powerful piece of drug legislation that gave the government authority to regulate the labeling of medicines. Essentially, this law required that drug labels accurately reflect the contents. Prior to this date, many labels did not contain any indication of the active ingredient within the bottle or its amount. Although the ingredients had to be accurately labeled, a drug could still be marketed for any disease.

In 1912, the Sherley Amendment to the PFDA prohibited the sale of drugs labeled with false therapeutic claims that were intended to defraud the consumer. A major

weakness, as borne out in subsequent legal battles, was the difficulty of proving that the false claim made by the seller was intentional.

It is surprising that up to this point in American history no attempt had been made to legislate the use of addictive drugs. The Harrison Narcotic Act of 1914 was passed to require prescriptions for high doses of narcotic drugs and to mandate that pharmacists and healthcare providers keep narcotic records. Since 1914, hundreds of additional state and federal laws have been passed to regulate drugs with abuse potential, including the landmark Comprehensive Drug Abuse Prevention and Control Act (see Section 2.8). Additional details on the history of the regulation of controlled substances are included in Chapter 27.

Unfortunately, two essential components were still missing from the regulation of drugs in the early 20th century. Although the PFDA and other legislation required that ingredients be listed on the label and prohibited intentional false claims, manufacturers did not have to prove that the drug was effective. Furthermore, product safety did not have to be tested before the drug was marketed. Bringing the issue to the forefront was an incident in 1937 in which an elixir of sulfanilamide containing a poisonous chemical (diethylene glycol) killed 107 people, mostly children.

In 1938, Congress passed the landmark Food, Drug, and Cosmetic Act (FDCA), which corrected certain loopholes in previous laws. This was the first law preventing the sale of newly developed drugs that had not been thoroughly tested for safety. Drug labels were required to contain instructions for safe use. The FDCA was also the first attempt at regulating cosmetics and medical devices. Unfortunately, the FDCA did not clearly define "prescription" or specify which drugs required a prescription. Most drugs, including many addictive and harmful substances, were sold by the corner druggist, sometimes legally, other times illegally. In 1951, the Durham-Humphrey Amendment to the FDCA delineated the difference between safer drugs, which were allowed to be sold OTC, and more dangerous drugs, which required prescriptions.

In the late 1950s, the drug thalidomide was found to produce severe birth defects in the children of women taking the drug as a sleeping pill and to treat morning sickness during pregnancy. Although the drug was not approved in the United States, it is estimated that over 20,000 Americans received the drug because it was widely distributed to healthcare providers without U.S. Food and Drug Administration (FDA) approval. As with other drug legislation, it took a tragedy to convince Congress to pass tougher regulations. Passage of the Kefauver-Harris Amendment to the FDCA in 1962 mandated that manufacturers prove their drugs were effective for specific purposes, as well as safe, through the conduct of "adequate and well-controlled" studies. This law was applied retroactively to all drugs introduced since the passage of the FDCA. This amendment also required that all significant adverse reactions be reported to the FDA and that complete information about adverse effects be included in literature distributed to healthcare providers. For the first time, informed consent was required from patients participating in experimental drug research.

The emphasis on effectiveness continued as the FDA contracted with the National Academy of Sciences and the National Research Council in 1966 to evaluate the effectiveness of 4000 drugs that were approved between 1938 and 1962 based only on their safety. Approximately 40% of all drugs introduced between 1938 and 1962 were found to be ineffective and were subsequently removed from the market. In 1972, a review of OTC drugs began to examine the safety and effectiveness of these products.

In the 1980s, the public placed considerable political pressure on the FDA to find drugs to treat rare or unusual disorders. Pharmaceutical companies were reluctant to develop drugs for these disorders because there would not be enough sales to recoup their research and development costs. To encourage development of such drugs, the Orphan Drug Act became law in 1983. An **orphan product** is a drug or biologic for treating rare diseases that affect fewer than 200,000 people in the United States. Drug manufacturers are now offered development grants, tax credits for clinical investigation expenses, and 7 years of exclusive marketing for an orphan drug. Over 600 medications have been approved as orphan drugs since the passage of this act (Pharmaceutical Processing World, 2019).

A major focus in the 1990s was to speed the drug approval process, which was often prolonged for many years. The Prescription Drug User Fee Act (PDUFA) of 1992 assessed fees from drug manufacturers to be used specifically for reducing the review time for new drug applications. The PDUFA was reauthorized in 1997 with the passage of the Food and Drug Administration Modernization Act, which also included provisions to accelerate the review of medical devices, regulate the advertising of unapproved uses of drugs, and regulate health claims for foods. The PDUFA has been reauthorized every 5 years. It is estimated that PDUFA fees collected in 2020 will amount to over $2.6 billion, accounting for approximately 40% of the total FDA budget (Congressional Research Service, 2020).

In reaction to the rising popularity of dietary supplements, Congress passed the Dietary Supplement Health and Education Act of 1994 to control misleading industry claims. Due in part to intense lobbying from the dietary supplement industry, the regulation of these products remains less stringent than that for prescription or OTC drugs. The regulation of herbal products and dietary supplements is discussed in detail in Chapter 7.

In early 2000, the focus of drug regulation turned to access. Advocacy groups claimed that the high cost of drugs caused unequal access to adequate healthcare for the poor, the uninsured, the underinsured, and older adults. In 2003, the Medicare Prescription Drug, Improvement, and Modernization Act (also called the Medicare Modernization

**Table 2.1** Historical Timeline of Regulatory Acts, Standards, and Organizations

| Year | Regulatory Acts, Standards, and Organizations |
|---|---|
| 1820 | Physicians establish the first comprehensive publication of drug standards, the *United States Pharmacopeia (USP)*. |
| 1848 | The Drug Importation Act requires that all drugs (as defined by the newly established pharmacopeia) entering the United States be inspected and analyzed for "quality, purity, and fitness for medical purposes." |
| 1852 | Pharmacists found the American Pharmaceutical Association (APhA). The APhA establishes the *National Formulary (NF)*, a standardized publication focusing on pharmaceutical ingredients. The USP continues to catalog all drug-related substances and products. |
| 1862 | The Federal Bureau of Chemistry, established under the administration of President Lincoln, eventually becomes the U.S. Food and Drug Administration (FDA). |
| 1902 | The Biologics Control Act controls the quality of sera and other blood-related products. |
| 1906 | The Pure Food and Drug Act prohibits the manufacture and sale of adulterated or misbranded foods, drugs, and medications. |
| 1912 | The Sherley Amendment makes medicines safer by prohibiting the sale of drugs labeled with false therapeutic claims. |
| 1914 | The Harrison Narcotics Act requires those who dispense opium, cocaine, and related substances to keep records of the drugs they dispense and makes it illegal to possess narcotics without a prescription. This act allows physicians to prescribe narcotics only for treatment, not to addicts. |
| 1938 | The Food, Drug, and Cosmetic Act is the first law preventing the marketing of drugs not thoroughly tested. |
| 1970 | The Comprehensive Drug Abuse Prevention and Control Act (also known as the Controlled Substances Act) organizes regulated drugs (including opiates, cocaine, cannabis, stimulants, depressants, and hallucinogens) into five schedules and imposes restrictions and penalties. |
| 1975 | The *United States Pharmacopeia* and *National Formulary* become a single standardized publication, the USP-NF. |
| 1986 | The Anti-Drug Abuse Act increases sentences and imposes mandatory minimum sentences for those convicted of illegal drug activity based on the type and quantity of drug involved. |
| 1986 | The Childhood Vaccine Act authorizes the FDA to acquire information about patients taking vaccines, to recall biologics, and to recommend civil penalties if guidelines regarding biologic use were not followed. |
| 1988 | The FDA is officially established as an agency of the U.S. Department of Health and Human Services. |
| 1992 | The Prescription Drug User Fee Act requires that nongeneric drug and biologic manufacturers pay fees to be used for improvements in the drug review process. |
| 1994 | The Dietary Supplement Health and Education Act requires clear labeling of dietary supplements and gives the FDA the power to remove supplements that cause a significant public risk. |
| 1997 | The FDA Modernization Act reauthorizes the Prescription Drug User Fee Act, representing the largest reform effort of the drug review process since 1938. |
| 2002 | The Best Pharmaceuticals for Children Act improves the safety and efficacy of medicines for children and continues the exclusivity provisions for pediatric drugs as mandated under the Food and Drug Administration Modernization Act of 1997. |
| 2003 | The Medicare Prescription Drug, Improvement, and Modernization Act provides older adults and those with disabilities a prescription drug benefit and better benefits under Medicare. |
| 2007 | The FDA Amendments Act (FDAAA) of 2007 reauthorizes and expands the Prescription Drug User Fee Act, the Modernization Act, the Best Pharmaceuticals for Children Act, and the Pediatric Research Equity Act. |
| 2009 | The Biologics Competition and Innovation Act of 2009 creates an abbreviated approval pathway for biosimilars and interchangeables |
| 2012 | The FDA Safety and Innovation Act (FDASIA) of 2012 reauthorizes the Prescription Drug User Fee Act. This requires the FDA to implement a structured benefit–risk framework in the new drug approval process. |
| 2020 | Over-the Counter Monograph Safety, Innovation and Reform Act of 2020 streamlines the process for approval of OTC medications |

Act) was passed. This Act created a new prescription drug benefit (called Medicare Part D) for seniors and younger people with disabilities. A brief timeline of major events in U.S. drug regulation is shown in Table 2.1.

# Drug Standards

## 2.3 The standardization of drug purity and strength is specified by the *United States Pharmacopeia-National Formulary*.

Until the 1800s, drugs were prepared from plants that were available in the natural environment. The strength and purity of the products varied considerably because they were entirely dependent on the experience (and integrity) of the druggist preparing the product and the quality of the local ingredients. Potency and safety varied from region to region and, indeed, from batch to batch. Consider the simple analogy of baking. If 100 people across the world were asked to bake a loaf of bread, the final products would vary considerably in size, taste, and nutritional value. It is likely that no two loaves would be the same. It is obvious that a standard recipe must be followed. Similarly, to obtain consistency in the preparation and potency of drugs, standards (recipes) are needed.

Among the first standards used by pharmacists was the **formulary**, or list of pharmaceutical products and drug recipes. In the United States, the first comprehensive publication of drug standards, the *United States Pharmacopeia (USP)*, was established in 1820. A **pharmacopeia** is a medical reference summarizing standards of drug purity, strength, and directions for synthesis. From 1852 until 1975, two major

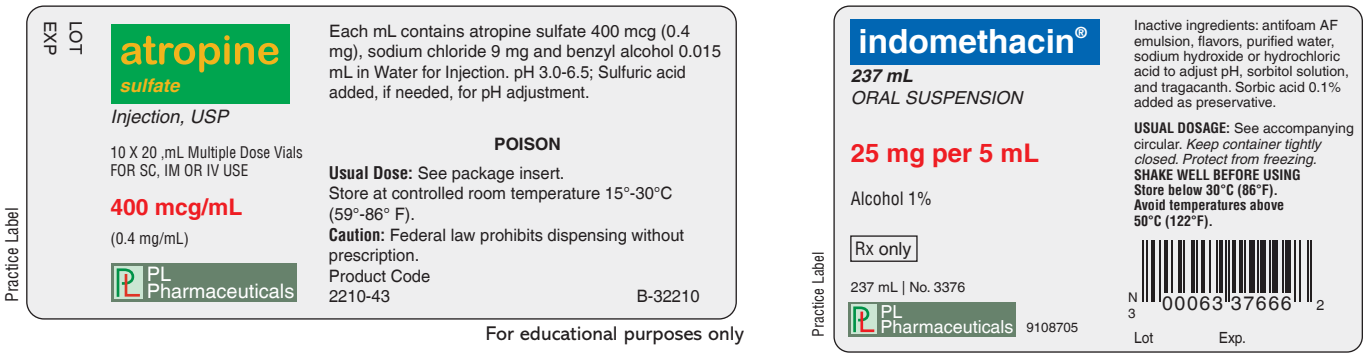


**Figure 2.2** Medication with the USP label (left) and without the USP label (right). Practice labels "for educational purposes only."

compendia maintained drug standards in the United States, the USP and the *National Formulary (NF)*. All drug products were covered in the USP, whereas the NF focused on non-drug ingredients. In 1975, the two were merged into a single publication named the *United States Pharmacopeia–National Formulary (USP-NF)*. Recent versions have contained more than 300 chapters and 4900 drug monographs. The USP-NF is published annually. Today, the USP label can be found on many medications verifying the purity and exact amounts of ingredients found within the container. Drugs marketed in the United States must conform to USP-NF standards to avoid possible charges of adulteration and misbranding. Sample labels are illustrated in Figure 2.2. The USP also provides a voluntary program for verifying the label accuracy of dietary supplements (see Chapter 7).

# The U.S. Food and Drug Administration

## 2.4 The regulatory agency responsible for ensuring that drugs and medical devices are safe and effective is the U.S. Food and Drug Administration.

The establishment of a regulatory agency for food and drugs in the United States began with a single chemist appointed by President Abraham Lincoln in 1862. The **U.S. Food and Drug Administration (FDA)** was established by the PFDA of 1906 and later expanded to carry out the provisions of the FDCA of 1938. It is one of the oldest drug regulatory agencies in the world. The FDA mission is:

- Protecting the public health by ensuring the safety, efficacy, and security of human and veterinary drugs, biologic products, medical devices, the nation's food supply, cosmetics, and products that emit radiation.
- Regulating the manufacturing, marketing, and distribution of tobacco products.
- Advancing the public health by helping to speed innovations that make medical products more effective, safer, and more affordable.
- Helping the public get the accurate, science-based information they need to use medical products and foods to maintain and improve their health.
- Ensuring the security of the food supply and fostering development of medical products to respond to deliberate and naturally emerging public threats.

With such an important and diverse mission, the FDA is organized around seven branches, as shown in Figure 2.3. The three that have the most importance to pharmacology are the Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER), and the Center for Food Safety and Applied Nutrition (CFSAN).

The mission of the CDER is to ensure the availability of safe, effective drugs; promote the safe use of marketed drugs; and ensure the quality and integrity of marketed drug products. All new drugs must be approved by the CDER before they can be marketed. This includes prescription drugs,

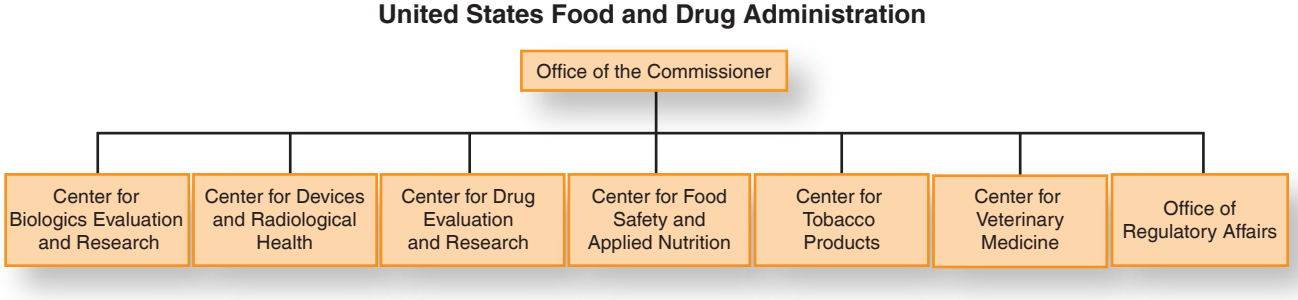


**Figure 2.3** Organization of the Food and Drug Administration showing the seven centers that regulate human and veterinary drugs, biologic products, medical devices, the nation's food supply, cosmetics, tobacco, and products that emit radiation.

OTC drugs, and all generic equivalents. After marketing, the CDER is responsible for continued monitoring of safety and may issue additional warnings to healthcare providers or consumers as additional information becomes available.

The CBER regulates the use of *biological products*, including vaccines, allergenics, tissues, cellular and gene therapies, vaccines, and blood. All new biological products are reviewed by the CBER and must be approved by this agency before marketing.

The CFSAN oversees the administration of herbal products, dietary supplements, and cosmetics. Although the CFSAN does not require testing of herbal products, dietary supplements, or cosmetics prior to marketing, the CFSAN is responsible for taking action against any of these products that are deemed unsafe or mislabeled.

Cosmetics are legally defined by the FDCA of 1938 as "articles intended to be rubbed, poured, sprinkled, or sprayed on, introduced into, or otherwise applied to the human body . . . for cleansing, beautifying, promoting attractiveness, or altering the appearance." Examples of products considered cosmetics are skin moisturizers, perfumes, lipsticks, fingernail polishes, eye and facial makeup preparations, shampoos, toothpastes, and deodorants. Can a product be both a cosmetic and a drug? In most cases, cosmetics are not drugs; however, it depends on a product's intended use. For example, if a shampoo is marketed to treat a condition such as dandruff, the active ingredient is considered a drug. If a skin cream claims to provide sunscreen protection, it may be considered a drug. Manufacturers of cosmetics are generally careful not to promote unwarranted therapeutic claims, such as that a product prevents or treats a condition or disease. This would cause the product to be considered a drug by the FDA and it would be subject to tighter regulations.

# Drug Approval

## 2.5 The drug approval process established by the U.S. Food and Drug Administration ensures that drugs sold in the United States are safe and effective.

Drugs are discovered in any number of ways. Penicillin was discovered purely by accident while the scientist was studying an unrelated topic. Many drugs have been isolated from natural substances, including plants and bacteria. Some medications are "me too" drugs, whereby the pharmacologist took a well-known drug and slightly modified the chemical structure to produce a very similar agent. As molecular biology and genetics have progressed into the modern era, drugs have been purposefully designed to fit into specific receptor sites on enzymes or cells.

Regardless of the path to discovery, all medications must be approved by the FDA before they can be sold in the United States. (Medical marijuana, discussed in Chapter 27, has become an exception to this approval process.) The FDA drug review and approval process follows a well-developed and organized plan, as summarized in Figure 2.4.

The first stage of drug development is **preclinical research**, which involves extensive laboratory testing by the pharmaceutical company. Scientists perform testing on human and microbial cells cultured in a laboratory. Studies include several species of animals to examine the drug's effectiveness at different doses and to look for adverse effects. The goals of this extensive testing on cells and in animals are to determine drug action and to predict whether the drug will cause harm to humans. Because laboratory tests do not accurately reflect the precise way the human body will respond to the drug, preclinical research results are always inconclusive. Most potential drugs do not proceed past the preclinical research stage because they are either too toxic or simply not effective. The FDA does not regulate preclinical testing.

If a drug appears promising, the pharmaceutical company submits an **Investigational New Drug (IND)** application to the FDA that contains all the animal and cell testing data. Scientists at the FDA examine the IND and must be convinced that the drug is safe enough to allow human testing. Approval from the FDA is necessary before human testing can begin.

Clinical investigation, the second stage of drug testing, takes place in three different stages termed **clinical phase trials**. These clinical trials are the longest part of the drug approval process and occur in sequential stages.

- **Phase 1.** Testing is conducted on 20 to 80 healthy volunteers for several months to determine proper dosage and to assess for adverse effects. The focus of the phase 1 trial is on *safety*. If unacceptable levels of toxicity are noted, the clinical trials are stopped.

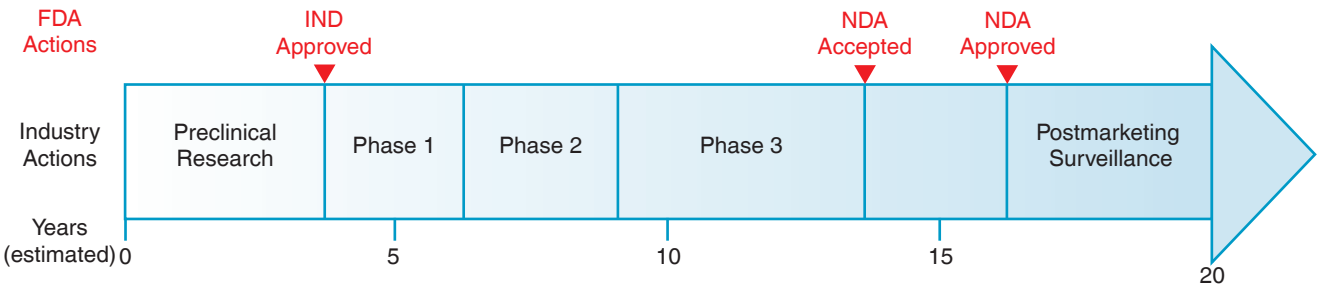


**Figure 2.4** Drug development timeline.

- **Phase 2.** In phase 2, an average 12 to 350 participants with the disease are treated with the experimental drug. The primary focus of the phase 2 trial is on *effectiveness*, although safety data continue to be recorded. In most cases, the effectiveness of the new drug is compared to an inert substance, or **placebo**, which serves as a control "nontreatment" group. In other cases, the new drug is compared to a standard drug used for the same condition. For example, a new drug for reducing fever may be compared to acetaminophen (Tylenol). If the new drug is found to have the same (or less) effectiveness and safety profile compared to the standard drug, the pharmaceutical company may stop the clinical trials. This phase may take several years.
- **Phase 3.** In phase 3, large numbers of patients with the disease are given the drug to determine variability of response in different populations. Potential drug–drug interactions are examined. Patients with chronic conditions such as cardiac, renal, or hepatic impairment are given the drug to determine safety in these important populations. Assessment of effectiveness and safety continues for several years, and the average number of patients varies from several hundred to about 3000.

If the drug continues to show promise through the clinical phase trials, a **New Drug Application (NDA)** is submitted to the FDA. The NDA signals that the pharmaceutical company is ready to market the new drug. During the NDA review, the FDA examines all preclinical and clinical data to assess whether the proposed drug is safe and effective. By law, the CDER is obligated to act on at least 90% of the NDAs for standard drugs within 10 months of submission. If the NDA is approved, the manufacturer may begin marketing the new drug. If the NDA is rejected, the FDA indicates whether the drug is "approvable" or "not approvable." "Approvable" means that the drug will likely be approved if the pharmaceutical company conducts additional testing or addresses specific issues identified by the FDA. A designation of "not approvable" indicates that the drug has significant barriers to approval.

Each year, the FDA approves a diverse range of new drugs and biological products. Some of the approved products, however, closely resemble existing medications and do not represent major advances in pharmacotherapy. A better way to track advances in drug therapy is to monitor how many of the approved drugs are **new molecular entities (NMEs)**, medications that are truly unique and structurally different from existing drugs (FDA, 2020c). From 2015 until 2019, the number of new molecular entities varied from 25 to 59 per year.

In the United States, the FDA grants the pharmaceutical company exclusive rights to name and market a drug for a certain number of years after it approves the NDA. During this period of **exclusivity**, competing companies are not allowed to market generic versions of the product (FDA, 2020b). The rationale for exclusivity is that the developing pharmaceutical company needs sufficient time to recoup the millions of dollars in research and development costs involved in designing and testing the new drug. Without the guarantee of exclusivity, pharmaceutical companies have little incentive to develop new and unique drugs. When exclusivity expires, competing companies may sell a generic equivalent drug, sometimes using a different name, which the FDA must approve. The typical length of exclusivity for a new drug is 5 years; however, this may be extended if the drug is determined to have a new indication, can be delivered by a different route, or is made available in a different dosage form. If, for example, a pharmaceutical company completes pediatric studies and determines the dosage and safety of a drug in this population, the FDA adds 6 months of exclusivity. Orphan drugs have 7 years of exclusivity. Expiration dates for the exclusivity of specific drugs are listed by the FDA in its *Approved Drug Products with Therapeutic Equivalence Evaluations* publication.

**Postmarketing surveillance**, stage 4 of the drug approval process, begins after the NDA review has been completed. The purpose of stage 4 testing is to assess for harmful drug effects in a larger population. Some adverse effects are very subtle, take longer to appear, and are not identified until a drug is prescribed for large numbers of people. Adverse drug reactions are reported by the manufacturers, healthcare providers, and patients to the FDA Adverse Event Reporting System (FAERS), a computerized database designed to support the FDA's postmarketing surveillance program.

The FDA holds public meetings annually to receive comments from patients, professional organizations, and pharmaceutical companies regarding the effectiveness and safety of new drug therapies. If the FDA discovers a serious problem, it will mandate that a drug be withdrawn from the market. Examples of successful postmarketing surveillance include the removal of two cholesterol-lowering drugs in 2016 because long-term clinical trials revealed that the medications were ineffective at reducing adverse cardiovascular events. In these cases, the withdrawals were not prompted by serious safety concerns. The benefits of the drugs were found to no longer outweigh their risks.

The drug approval process has several important limitations. Historically, drug trials have used White men as their test population. Because gender and racial differences may affect how drugs are handled by the body, pharmaceutical companies are now including a more diverse population in their clinical trials. Most drugs have not been tested in children: Pediatric doses and responses

are often based on experience rather than research data. Although clinical trials test drugs in pregnant laboratory animals and examine for possible birth defects, these data may not be representative of how drugs affect pregnant women or their fetuses. Finally, adverse effects may occur at such a low level that they are statistically insignificant in clinical trials using a few thousand patients. Several million patients may need to take the drug before these effects can be identified.

Another limitation of the drug approval process relates to off-label uses. A new drug is always approved for a *specific indication* at doses that are demonstrated to be safe and effective. After several years of clinical experience, however, healthcare providers may find that the drug is also useful for indications not approved by the FDA. Or, the prescriber may find that the drug works better at a different dosage level or by a different route of administration. Once initially approved by the FDA, *healthcare providers may legally prescribe the drug for any indications* they feel are appropriate, despite the fact that the drug was never tested or approved for these additional conditions. How widespread is off-label prescribing? It is estimated that over 20% of prescriptions are for indications not approved by the FDA (Agency for Healthcare Research and Quality, 2020). The use of off-label drugs is particularly prevalent in cancer treatment and in pediatric patients (Yackey et al., 2019). The FDA prohibits pharmaceutical companies from advertising or promoting their drugs for off-label uses.

**PharmFACT**

The median cost for research and development to bring a new drug to market is $985 million. (Wouters et al., 2020).

**CONNECTION Checkpoint 2.1**

In 2016, granisetron (Sustol), an antiemetic drug, and daclizumab (Zinbryta), an interleukin-2 blocking monoclonal antibody for treating relapsing multiple sclerosis, were approved. Are these considered therapeutic or pharmacologic classifications?

# Changes to the Drug Approval Process

## 2.6 The U.S. Food and Drug Administration has sped up the process of drug review.

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

With the high expenses associated with development of a new drug, pharmaceutical companies are justifiably anxious to get the drug marketed. The public is also anxious to receive new medications, particularly for diseases that have a high mortality rate. Although the criticisms of government regulatory agencies are certainly understandable, the fundamental priority of the FDA is to ensure the safety of medications. Without an exhaustive review of scientific data, the public could be exposed to dangerous or ineffective drugs.

In 1992 and in 2012, legislation was passed to allow the FDA to speed up the review and approval of drugs intended to treat serious conditions. The following are four strategies used by the FDA to accelerate the review process (FDA, 2010a).

- **Fast track.** A fast track designation means that the new drug has the *potential* to meet an unmet need for a condition in which there is no current therapy, or the drug may offer significant improvement over existing therapies. The request for a fast track is made by the pharmaceutical company and the designation is reviewed by the FDA within 60 days.
- **Breakthrough therapy.** A breakthrough therapy means that trials suggest there is *clinical evidence* that the drug may demonstrate substantial improvement over existing therapies for a serious or life-threatening condition. Like the fast track, a request for a breakthrough therapy designation is made by the pharmaceutical company and reviewed by the FDA within 60 days.
- **Priority review.** When an NDA is received, the FDA makes a decision to perform a standard review (average 10 months) or a priority review (average 6 months). The decision is based on whether the new drug would offer a significant improvement over existing therapies for a serious condition.
- **Accelerated approval.** It may take many years to demonstrate that a drug provides real clinical benefit: improved patient survival or how a patient feels or functions. In these cases, the FDA may approve the drug based on "intermediate clinical endpoints." The best example is a new anticancer drug. The new drug may show positive evidence of tumor shrinkage in clinical trials and receive accelerated approval based on this evidence. The new drug can be marketed at this point. However, it may take several years before it is known whether the drug actually improves patient survival. The drug company can continue to market the new drug, but must perform follow-up studies, known as *confirmatory trials*. If the confirmatory trials show the drug did not improve survival, the FDA may withdraw the accelerated approval.

# Prescription and Over-the-Counter Drugs

## 2.7 Over-the-counter drugs are usually safe and effective when used according to label instructions.

The 1951 Durham-Humphrey Amendment to the FDCA clearly established the difference between prescription and OTC drugs. To obtain a prescription drug, an order must be given authorizing the patient to receive the medication. Prescription medications are judged by the FDA to be potentially addictive or too harmful for self-administration. In some cases, they are used to treat conditions too complex for self-diagnosis by the consumer or the drug may require a skilled nurse or healthcare provider to administer it.

The advantages of requiring a prescription are numerous. The healthcare provider has an opportunity to examine the patient and determine a specific diagnosis. The prescriber can maximize therapy by ordering the proper drug for the patient's condition and by controlling the amount and frequency of the drug to be dispensed. In addition, the healthcare provider has an opportunity to teach the patient proper use of the drug and its expected adverse effects.

In contrast to prescription drugs, OTC drugs do not require an order from a healthcare provider. In most cases, patients may treat themselves safely if they carefully follow instructions included with the medication. A key point to remember is that no drug is without risk; if patients do not follow the guidelines on the label, serious adverse effects may result.

Patients prefer to take OTC medications for many reasons. OTC drugs are obtained more easily than prescription drugs. No appointment with a healthcare provider is required, thus saving time and money. Without the assistance of a healthcare provider, however, choosing the proper medication for a specific problem can be challenging. OTC drugs may interact with foods, herbal products, prescription drugs, or other OTC drugs. Patients may not be aware that some OTC medications can impair their ability to function safely. Self-treatment is sometimes ineffective, and the potential for harm may increase if the disease is allowed to progress.

The approval process for an OTC product differs from prescription products and may proceed by several paths. The manufacturer may choose to submit an NDA, as described in Section 2.5. However, the company may instead choose to switch a prescription product to an OTC product. In these cases, the FDA reviews existing consumer data to assess drug safety. Products that have changed from prescription to OTC include nicotine patches and gum, famotidine (Pepcid AC), cimetidine (Tagamet HB), omeprazole (Prilosec), cetirizine (Zyrtec), budesonide (Rhinocort), fluticasone (Flonase), and loratadine (Claritin).

An additional path for OTC product approval involves **drug monographs** prepared by the FDA. For OTC products previously approved by the FDA, the detailed monographs describe the active ingredient, its acceptable forms (e.g., capsule, liquid, topical cream), dosages or concentrations, and required labeling. Manufacturers may market an OTC drug *without preapproval of the FDA* if the product falls within the parameters described in the monograph (FDA, 2020d). In 2020 Congress passed the Over-the Counter Monograph Safety, Innovation and Reform Act, which makes it easier to revise monographs so they include up-to-date safety data, dosage changes, and other innovative changes to these medications (Pew Charitable Trust, 2020).

Herbal products and dietary supplements are also widely available OTC. Herbal products and dietary supplements are not considered drugs; they are not marketed to treat any disease, and they are not subject to the same regulatory process as medications. Yet some of these products can cause adverse effects and interact with medications.

### CONNECTIONS: Lifespan Considerations

#### The Association of Cost-Related Medication Nonadherence and Food Insecurity in Older Adults

It is known that the cost of prescription drugs may be a major cause for medication nonadherence in the older adult, but are there other factors that impact nonadherence? Studies suggest that *food insecurity*—the lack of access to sufficient, nutritious, and affordable food—may also predict nonadherence (Afulani et al., 2015; Herman et al., 2015). Afulani et al. (2015) found that as the severity of food insecurity increased, nonadherence also increased. Older adult women and older adults with chronic conditions were more likely to report nonadherence. However, having insurance coverage, particularly Medicare and Medicaid, decreased nonadherence. Food security-related nonadherence is not just a problem for the older adult. Herman et al. (2015) found a similar relationship in the nonelderly adult population. In that study, female adults and adults with chronic conditions, low income, no or insufficient health insurance, severe mental illness, or functional limitations had an increased risk of cost-related medication nonadherence.

Nurses should assess factors other than cost that may increase the risk of nonadherence, particularly food insecurity. Recognizing that patients who are unable to afford or access adequate and nutritious food places them at risk for medication nonadherence may help the healthcare team improve health.

Nurses should always inquire about their patients' use of herbal products and dietary supplements and caution them that the FDA has not tested these products for effectiveness or safety (see Chapter 7).

# Drug Schedules

## 2.8 Drugs with a potential for abuse are categorized into schedules.

**Dependence** is a powerful physiologic or psychologic need for a substance. Some drugs are frequently abused or have a high potential for dependence; thus, the selling and distribution of these drugs are highly restricted. Drugs that have a significant potential for abuse are placed into five categories called *schedules*. These **scheduled drugs** are classified and regulated according to their potential for abuse, as shown in Table 2.2. Concepts of dependence and drug schedules are discussed in detail in Chapter 27.

In the United States, **controlled substances** are drugs whose use is restricted by the Comprehensive Drug Abuse Prevention and Control Act of 1970 and its later revisions. Every healthcare provider or entity that produces, distributes, dispenses, or prescribes such substances must register with the Drug Enforcement Administration (DEA). Registrants must maintain complete records of all quantities purchased and sold and report suspicious orders of unusual size or frequency. Drugs with the highest abuse potential have additional restrictions. For example, providers must use a special order form to obtain Schedule II drugs, and orders must be written and signed by the provider. Telephone orders to a pharmacy are not permitted. Refills for Schedule II drugs are not permitted; patients must visit their healthcare provider to receive a new prescription. Healthcare providers convicted of unlawful manufacturing, distributing, and dispensing of controlled substances face severe penalties.

**CONNECTION Checkpoint 2.2**

Once a new drug is approved, it is assigned names. What are the two basic types of drug names and who assigns them?

# Prescriptive Authority for Nurses

## 2.9 Advanced practice nurses are helping to fill the primary care workforce gap.

*The Future of Nursing: Leading Change, Advancing Health* identified that the changing healthcare landscape, the changing profile of the U.S. population, and notable shortage of primary care health professionals in the United States would require fundamental shifts in the care delivery system (Institute of Medicine, 2011). In particular, the report suggested that advanced practice registered nurses (APRNs), if permitted to practice to the full extent of their education and training, could help build the workforce necessary to meet the country's primary care needs and contribute their unique skills to the delivery of patient-centered, community-based healthcare. At least twenty-two states plus Washington, D.C., the Veterans Administration, and Indian Health Services grant nurse practitioners (NPs) the right to practice to the top of their education without physician oversight. Today the APRN is viewed as an essential member of the healthcare system's ability to deliver affordable care.

NPs hold prescriptive privileges, including controlled substances, in all 50 states and D.C. According to the 2019 AANP National Nurse Practitioner Sample Survey, nurse practitioners in full-time practice write an average of 20 prescriptions per day (American Association of Nurse Practitioners, 2020). The ability to prescribe drugs, a key component of most treatment plans, ensure that patients are provided the best and most cost-effective care possible. This text includes a focus on preparing for prescriptive authority, and Connections features detail specific information the APRN needs to know to prepare for this authority.

**Table 2.2** U.S. Drug Schedules and Examples

| Drug Schedule | Abuse Potential | Examples | Therapeutic Use |
|---|---|---|---|
| I | Highest | Heroin, GHB, LSD, marijuana, MDMA, mescaline, methaqualone, methcathinone, peyote, and psilocybin | No currently acceptable medical use; high potential for abuse |
| II | High | Potent opioids (such as codeine in high doses, fentanyl, methadone, morphine, oxycodone, meperidine), amphetamine, cocaine, methamphetamine, methylphenidate, PCP, and short-acting barbiturates | Have currently accepted medical use but use may be severely restricted; normally no refills are permitted (but there are exceptions) |
| III | Moderate | Anabolic steroids, buprenorphine ketamine, codeine (less than 90 mg per dosage unit), hydrocodone (lower doses compounded with aspirin or acetaminophen), and intermediate-acting barbiturates | Have currently accepted medical use; less stringent controls than Schedule II drugs; five refills allowed in a 6-month period |
| IV | Low | Benzodiazepines (such as alprazolam, diazepam, midazolam, temazepam), long-acting barbiturates, meprobamate, pentazocine, tramadol, and zolpidem | Have currently accepted medical use; similar controls to Schedule III drugs; five refills allowed in a 6-month period |
| V | Lowest | Cough medicines with codeine, antidiarrheal medicines with small amounts of opioids | Have currently accepted medical use; similar controls to Schedule III and IV drugs |

Controlled Substance Schedules, U.S. Department of Justice, n.d. Retrieved from http://www.deadiversion.usdoj.gov/schedules.

# Understanding Chapter 2

## Key Concepts Summary

**2.1** Early American history saw the rise of patent medicines and the lack of adequate drug regulations.

**2.2** In the 1900s, drug legislation was enacted to make drugs safer and more effective.

**2.3** The standardization of drug purity and strength is specified by the *United States Pharmacopeia-National Formulary*.

**2.4** The regulatory agency responsible for ensuring that drugs and medical devices are safe and effective is the U.S. Food and Drug Administration.

**2.5** The drug approval process established by the U.S. Food and Drug Administration ensures that drugs sold in the United States are safe and effective.

**2.6** The U.S. Food and Drug Administration has sped up the process of drug review.

**2.7** Over-the-counter drugs are usually safe and effective when used according to label instructions.

**2.8** Drugs with a potential for abuse are categorized into schedules.

**2.9** Advanced practice nurses are helping to fill the primary care workforce gap.

## CASE STUDY: Making the Patient Connection

**Remember the patient "Gertrude Stone" at the beginning of the chapter? Now read the remainder of the case study. Based on the information presented within this chapter, respond to the critical thinking questions that follow.**

Gertrude Stone lives alone in the house she has owned for 46 years. Although she is seldom sick, when she needs to see a healthcare provider, she must ride the public bus system. The trip requires two bus transfers and can be tiring.

Because Gertrude lives only one block from a grocery store, she often self-medicates using OTC drugs. She strongly believes in the use of herbs, vitamins, and home remedies.

As a parish nurse, you are organizing a community health fair at the church where Gertrude is an active member.

### Critical Thinking Questions

1. How would you counsel Gertrude about the safety of OTC drugs?
2. What are the advantages and disadvantages of OTC medications?
3. How can Gertrude be certain that OTC medications are safe for her?

## Additional Case Study

Your 12-year-old nephew is preparing a report for school about the FDA and the drug approval process. You, as a healthcare provider, are often called on by family members to answer questions about anything health related. Following are his questions. How would you respond?

1. What is the role of the FDA?
2. What role does the FDA play in regulating herbal and dietary supplements?
3. How quickly can a new drug be approved by the FDA?

*Answers to Additional Case Study questions are available on the faculty resources site. Please consult with your instructor.*

## Chapter Review

1. The governmental drug legislation requires the drug manufacturer to prove that a drug is both safe and:
    1. Free of adverse effects and potential reactions.
    2. Effective for a specified purpose.
    3. Reasonable in cost and easily accessible.
    4. Beneficial to various population groups.
2. The drug research participant with a particular disease is taking part in an investigative study to examine the effects of a new drug. Previously, this drug was tested using healthy volunteers. The next phase of the clinical trial investigation in which the patient will be participating is:
    1. Phase 1
    2. Phase 2
    3. Phase 3
    4. Phase 4
3. A drug that is being prescribed "off-label" means that the drug:
    1. Is available in Europe or Canada but not in the United States.
    2. Has FDA approval for one use but is being prescribed for another purpose.
    3. Is under an accelerated approval process and full indications have not yet been discovered.
    4. Is a generic drug being used instead of a trade-name drug.
4. The patient requests that a refill prescription of a Schedule II controlled substance be telephoned to the drug store. When responding to the patient, you would consider which factor? Refills of Schedule II drugs:
    1. Are less costly than the original prescription.
    2. Must be listened to by at least two people.
    3. Are verified through the local DEA office.
    4. Are not permitted under federal law.
5. In 1992 and in 2012, legislation was passed to allow the FDA to speed up the review and approval of drugs intended to treat serious conditions. When would the following accelerated review processes be applicable?
    1. Fast track
    2. Breakthrough therapy
    3. Priority review
    4. Accelerated approval
6. While in the clinic, you note that multiple patients had a reaction to the same medication, a drug that has been available for several years. Which action should you take? (Select all that apply.)
    1. File an Adverse Event Report with the FDA.
    2. Note the reaction in the patient's chart.
    3. Notify the healthcare provider who ordered the drug.
    4. Wait until the FDA sends a notification of the drug's recall before informing the patient.
    5. Compare each patient's reaction to determine if it is the same.

*See Appendix A for answers to critical thinking questions, case study questions and review questions.*

## References


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