Levent Ince/Getty Images

Pharmacology

An Introduction

8th edition

Henry Hitner, Ph.D.

Professor Emeritus
Department of Neuroscience, Physiology, and Pharmacology
Philadelphia College of Osteopathic Medicine
Philadelphia, Pennsylvania

Adjunct Professor, Pharmacology
Physician Assistant Program
Drexel University
Philadelphia, Pennsylvania

Barbara Nagle, Ph.D.

President
Clinical Research Development and Education
III Associates
Bryn Mawr, Pennsylvania

Michele B. Kaufman, PharmD, BCGP

Pharmacist
NewYork-Presbyterian Hospital Lower Manhattan
New York, New York

Hannah (Cooke) Ariel, PharmD

Adjunct Instructor
Chemistry and Biochemistry
Queens College
Queens, New York

Yael Peimani-Lalehzarzadeh, PharmD

Long Island, New York

Mc Graw Hill

PHARMACOLOGY: AN INTRODUCTION, EIGHTH EDITION

This book is printed on acid-free paper.

1 2 3 4 5 6 7 8 9 LWI 24 23 22 21

ISBN 978-1-260-02182-0 (bound edition)
MHID 1-260-02182-3 (bound edition)
ISBN 978-1-260-47051-2 (loose-leaf edition)
MHID 1-260-47051-2 (loose-leaf edition)

Portfolio Manager: *Marah Bellegarde*
Product Developer: *Theresa Collins; Joan Weber*
Marketing Manager: *To come*
Content Project Managers: *Sandy Wille; Rachael Hillebrand*
Senior Buyer: *Sandy Ludovissy*
Senior Designer: *Matt Diamond*
Content Licensing Specialist: *Lorraine Buczek*
Cover Image: *Ingram Publishing/SuperStock*
Compositor: *SPi Global*

All credits appearing on page or at the end of the book are considered to be an extension of the copyright page.

Library of Congress Cataloging-in-Publication Data

Names: Hitner, Henry, author. | Nagle, Barbara T., author. | Kaufman, Michele B., author. | Ariel, Hannah (Cooke), author. | Peimani-Lalehzarzadeh, Yael, author.

Title: Pharmacology : an introduction / Henry Hitner, Ph.D., Professor Emeritus Department of Neuroscience, Physiology, and Pharmacology, Philadelphia College of Osteopathic Medicine, Philadelphia, Pennsylvania, Adjunct Professor, Pharmacology Physician Assistant Program, Drexel University, Philadelphia, Pennsylvania, Barbara Nagle, Ph.D., President. Clinical Research Development and Education, III Associates, Bryn Mawr, Pennsylvania, Michele B. Kaufman, PharmD, BCGP, Pharmacist New York-Presbyterian Hospital Lower Manhattan, New York, New York, Hannah (Cooke) Ariel, PharmD, Adjunct Instructor, Chemistry and Biochemistry, Queens College, Queens, New York, Yael Peimani-Lalehzarzadeh, PharmD, Long Island, New York.

Description: 8th edition. | New York, NY : McGraw Hill Education, [2022] | Includes index. | Audience: Ages 18+

Identifiers: LCCN 2020045389 (print) | LCCN 2020045390 (ebook) | ISBN 9781260021820 (paperback) | ISBN 9781260470543 (epub)

Subjects: LCSH: Pharmacology.

Classification: LCC RM300 .H57 2022 (print) | LCC RM300 (ebook) | DDC 615.1—dc23

LC record available at https://lccn.loc.gov/2020045389
LC ebook record available at https://lccn.loc.gov/2020045390

mheducation.com/highered

Brief Contents

About the Authors xviii

Preface xx

What Every Student Needs to Know xxvi

1. Pharmacology: An Introduction 4
2. Pharmacokinetics and Factors of Individual Variation 17
3. Geriatric Pharmacology 34
4. Math Review and Dosage Calculations 43
5. Introduction to the Autonomic Nervous System 58
6. Drugs Affecting the Sympathetic Nervous System 68
7. Drugs Affecting the Parasympathetic Nervous System 85
8. Drugs Affecting the Autonomic Ganglia 99
9. Skeletal Muscle Relaxants 106
10. Local Anesthetics 123
11. Introduction to the Central Nervous System 138
12. Sedative-Hypnotic Drugs and Alcohol 146
13. Antipsychotic and Antianxiety Drugs 161
14. Antidepressants, Psychomotor Stimulants, and Lithium 175
15. Psychotomimetic Drugs of Abuse 188
16. Antiepileptic Drugs 200
17. Antiparkinson Drugs and Alzheimer's Disease Drugs 212
18. General Anesthetics 225
19. Opioid Analgesics 248
20. Nonopioid Analgesics, Nonsteroidal Anti-inflammatories, and Antigout Drugs 272
21. Review of Cardiac Physiology and Pathology 304

spxChrome/Getty Images

22. Treatment of Heart failure 312
23. Antiarrhythmic Drugs 326
24. Antianginal Drugs 341
25. Diuretics 352
26. Antihypertensive Drugs 373
27. Anticoagulants and Coagulants 388
28. Nutrition and Therapy 409
29. Hypolipidemic Drugs 431
30. Hematinics 451
31. Antihistamines and Mast Cell Stabilizers 468
32. Respiratory Pharmacology, Treatment of Asthma and COPD 485
33. Therapy of GI Disorders: Peptic Ulcers, GERD, and Vomiting 502
34. Agents That Affect Intestinal Motility 529
35. Introduction to the Endocrine System 546
36. Adrenal Steroids 557
37. Gonadal Hormones, Oral Contraceptives, and Erectile Dysfunction Drugs 575
38. Drugs Affecting the Thyroid and Parathyroid Glands and Bone Degeneration 601
39. Pancreatic Hormones and Antidiabetic Drugs 620
40. Posterior Pituitary Hormones: Antidiuretic Hormone and Oxytocin 653
41. Antibacterial Agents 666
42. Antifungal and Antiviral Drugs 687
43. Parasitic Infections: Antiprotozoal and Anthelmintic Drugs 721
44. Antiseptics and Disinfectants 737
45. Antineoplastic Agents and Oncology Immunotherapy 754
46. Immunopharmacology 771

Glossary 785

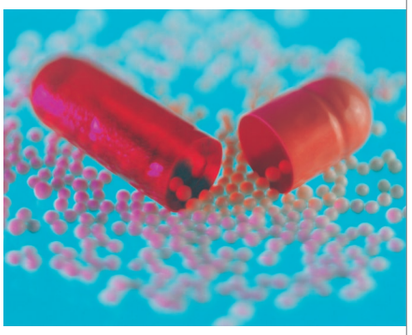
Appendix A Latin Abbreviations Used in Medicine 800

Appendix B Abbreviations and Symbols Commonly Used in Medical Notations 801

Index 805

Table of Contents

PART 1
General Concepts 3


Digital Vision/SuperStock

CHAPTER 1

Pharmacology: An Introduction 4

- Drug Sources and Major Areas of Pharmacology 5
- Terminology Related to Drug Effects 6
- Basic Concepts in Pharmacology 7
- Dose-Response and Time-Plasma Drug Concentration Curves 8
- Drug Safety 9
- Drug Nomenclature 10
- Drug References and Drug Legislation 10
- *Chapter Review 13*

CHAPTER 2

Pharmacokinetics and Factors of Individual Variation 17

- Drug Forms and Routes of Administration 18
- Pharmacokinetic Processes 20
- Clinical Factors that Determine the Intensity of Drug Response 23
- Factors of Individual Variation 25
- Pharmacokinetic Considerations for Pediatrics 26
- Drug Interactions 28
- Terminology Associated with Chronic Drug Use and Abuse 28
- *Chapter Review 30*

CHAPTER 3

Geriatric Pharmacology 34

- Drug Use in the Elderly 35
- Drug Absorption and Distribution 35
- Drug Metabolism and Excretion 36
- Effects of Age on Drug Response 37
- Drug Compliance in the Elderly 38
- *Chapter Review 40*

CHAPTER 4

Math Review and Dosage Calculations 43

- Fractions, Decimals, and Percents 44
- Dosage Calculations 46

Systems of Measurement 46
Calculating Dosages 48
Pediatric Dosage Calculations 49
Monitoring IV Infusion Rates 50
Chapter Review 52

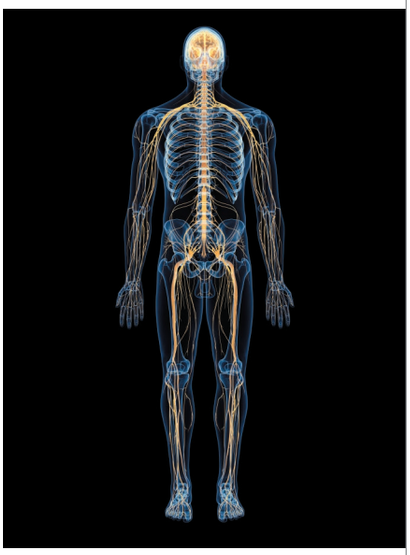
PART 2

Pharmacology of the Peripheral Nervous System 57

CHAPTER 5
Introduction to the Autonomic Nervous System 58
Nervous System Organization 59
Overview of the ANS 60
Parasympathetic and Sympathetic Divisions 60
ANS Nerve Fibers and Neurotransmitters 63
Cholinergic and Adrenergic Receptors 65
Chapter Review 66

CHAPTER 6
Drugs Affecting the Sympathetic Nervous System 68
Adrenergic Nerve Endings 69
Adrenergic Receptors 70
Adrenergic Drug Classes 71
Alpha-Adrenergic Drugs 72
Beta-Adrenergic Drugs 73
Alpha-Adrenergic Blocking Drugs 75
Beta-Adrenergic Blocking Drugs 76
Adrenergic Neuronal Blocking Drugs 78
Chapter Review 82

CHAPTER 7
Drugs Affecting the Parasympathetic Nervous System 85
Cholinergic Nerve Activity 86
Cholinergic Receptors 86
Cholinergic Drugs 88
Clinical Indications for Anticholinesterase Drugs 91
Anticholinergic Drugs 93
Preferred Treatment for Selected Conditions 95
Chapter Review 96



Sebastian Kaulitzki/Shutterstock

CHAPTER 8

Drugs Affecting the Autonomic Ganglia 99

- Ganglionic Stimulants 100
- Drugs Used in Smoking Cessation 100
- Ganglionic Blockers 102
- Drug Interactions with Ganglionic Blocking Drugs 103
- *Chapter Review 104*

CHAPTER 9

Skeletal Muscle Relaxants 106

- Skeletal Muscle Relaxation 108
- Peripherally Acting Skeletal Muscle Relaxants 108
- Major Adverse Effects Associated with Peripheral Neuromuscular Blockers 112
- Direct-Acting Skeletal Muscle Relaxants 114
- Centrally Acting Skeletal Muscle Relaxants (Spasmolytics) 115
- Preferred Treatment for Selected Conditions 117
- *Chapter Review 120*

CHAPTER 10

Local Anesthetics 123

- How Local Anesthetics Work 124
- Types of Local Anesthetics 125
- Types of Local Anesthesia 126
- Adverse Effects Associated with Local Anesthetics Use 130
- Clinical Applications 130
- Special Considerations 131
- *Chapter Review 133*

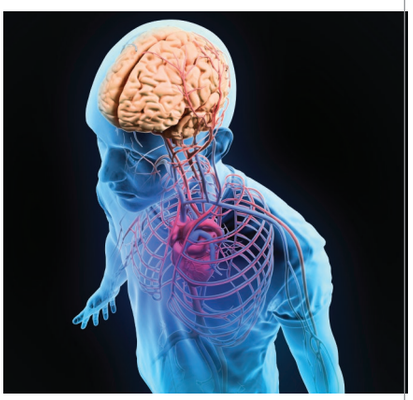
PART 3

Pharmacology of the Central Nervous System 137

CHAPTER 11

Introduction to the Central Nervous System 138

- Structural and Functional Features of the Brain 139
- Diencephalon and Brainstem 140
- Cerebellum 141
- Spinal Cord 141
- Functional Components 141
- *Chapter Review 143*



Shutterstock / Mopic

CHAPTER 12

Sedative-Hypnotic Drugs and Alcohol 146

- Sleep Cycle 148
- Mechanism of Action of Sedative-Hypnotic Drugs 148
- Barbiturate Sedatives and Hypnotics 149
- Benzodiazepines 152
- Miscellaneous Hypnotic Drugs 154
- Alcohol 155
- *Chapter Review 158*

CHAPTER 13

Antipsychotic and Antianxiety Drugs 161

- Antipsychotic Drugs 162
- Phenothiazines 163
- Butyrophenones 164
- Thioxanthenes 165
- Atypical Antipsychotic Drugs 166
- Antianxiety Drugs 167
- *Chapter Review 172*

CHAPTER 14

Antidepressants, Psychomotor Stimulants, and Lithium 175

- Types of Depression 176
- Selective Serotonin Reuptake Inhibitors 177
- Serotonin-Norepinephrine Reuptake Inhibitors 178
- Tricyclic Antidepressants 179
- Monoamine Oxidase Inhibitors 180
- Antidepressants with Additional Mechanisms of Action 182
- Psychomotor Stimulants 182
- Lithium 183
- Preferred Therapy for Depression, Mania, and Bipolar Disorder 184
- *Chapter Review 185*

CHAPTER 15

Psychotomimetic Drugs of Abuse 188

- LSD-Type Hallucinogens 189
- Psychomotor Stimulants 191
- Phencyclidine 194
- Marijuana 194
- *Chapter Review 197*

CHAPTER 16

Antiepileptic Drugs 200

Types of Epilepsy 201

Drugs Effective for Both Generalized Tonic—Clonic and Partial Seizures 202

Drugs Effective Primarily for Partial Seizures 206

Drugs Used in the Treatment of Absence Seizures 206

Treatment of Status Epilepticus 207

Preferred Therapy for Epileptic Seizures 207

Chapter Review 209

CHAPTER 17

Antiparkinson Drugs and Alzheimer's Disease Drugs 212

Neurotransmitters Affecting the Basal Ganglia 213

Drugs that Form Dopamine 215

Drugs that Inhibit Metabolism of Levodopa and Dopamine 216

Dopamine Receptor Agonists 219

Miscellaneous Drugs 219

Preferred Therapy for Parkinson's Disease 220

Alzheimer's Disease 221

Chapter Review 222

CHAPTER 18

General Anesthetics 225

Types of Anesthesia 227

Characteristics of General Anesthesia 228

Mechanism of Action of General Anesthetics 229

Classes of General Anesthetics 230

Nonanesthetic Effects of General Anesthetics 236

Adjunct Medications Used in General Anesthesia 239

Special Considerations with General Anesthetic Use 242

Preferred Use of Anesthetics 244

Chapter Review 245

CHAPTER 19

Opioid Analgesics 248

Pathways for Pain Recognition 250

Clinical Indications 251

Opioid Analgesics 251

Sites and Mechanism of Opioid Action 253

Nonanalgesic Opioid Effects 256

Drug Administration and Disposition 258

Adverse Effects, Cautions, and Contraindications 259
Treatment of Physical Dependence and Respiratory Depression 260
Opioid Antitussives 263
Chapter Review 268

CHAPTER 20

Nonopioid Analgesics, Nonsteroidal Anti-inflammatories, and Antigout Drugs 272

Mediators of Inflammation 273
Drugs that Suppress Inflammation 276
Clinical Indications 279
Actions of Nonopiod Anti-inflammatory Analgesics 279
Adverse Effects, Toxicities, and Contraindications 287
Drugs Useful in Treating Gout 290
Chapter Review 297

PART 4

Pharmacology of the Heart 303

CHAPTER 21

Review of Cardiac Physiology and Pathology 304

Cardiac Muscle 305
Conduction System 305
The Electrocardiogram 307
Cardiac Nerve Supply 307
Main Diseases of the Heart 308
Chapter Review 309

CHAPTER 22

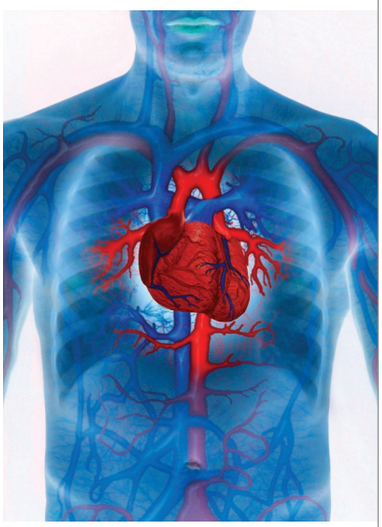
Treatment of Heart Failure 312

Chronic Heart Failure 313
Diuretic Therapy of CHF 314
Vasodilator Therapy of CHF 316
Use of Adrenergic Beta-Blockers in CHF 317
Cardiac Glycosides 318
Chapter Review 323

CHAPTER 23

Antiarrhythmic Drugs 326

Types of Arrhythmias 327
Electrophysiology of the Heart 329



Don Farrall/Digital Vision/Getty Images

Class 1 Antiarrhythmic Drugs: Sodium Channel Blockers 331
Class 2 Antiarrhythmic Drugs: Beta-Blockers 333
Class 3 Antiarrhythmic Drugs: Potassium Channel Blockers 334
Class 4 Antiarrhythmic Drugs: Calcium Channel Blockers 334
Special Considerations and Preferred Therapy for Selected Arrhythmias 336
Chapter Review 338

CHAPTER 24

Antianginal Drugs 341
Classification of Angina Pectoris 342
Nitrates 343
Beta-Adrenergic Blocking Drugs 345
Calcium Channel Blockers 346
Preferred Therapy for Treatment of Angina Pectoris 347
Chapter Review 348

PART 5

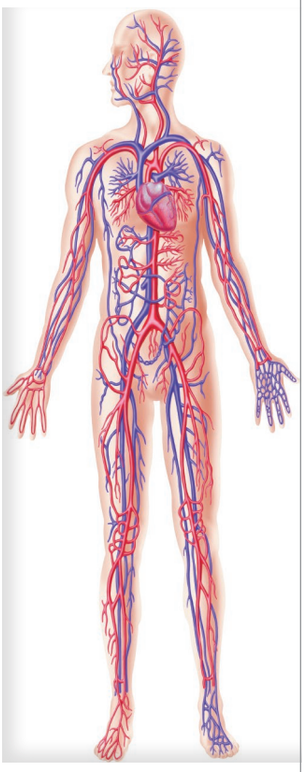
Pharmacology of the Vascular and Renal Systems 351

CHAPTER 25

Diuretics 352
Clinical Indications for Diuretic Use 354
Renal Physiology and Conditions Associated with Renal Dysfunction 354
Osmotic Diuretics 359
Carbonic Anhydrase Inhibitors 359
Thiazide and Thiazide-Like Diuretics 362
Organic Acid (Loop) Diuretics 363
Potassium-Sparing Diuretics 365
ADH Antagonists and Miscellaneous Diuretics 365
Preferred Treatment, Adverse Effects, and Drug Interactions 366
Chapter Review 370

CHAPTER 26

Antihypertensive Drugs 373
Physiologic Factors that Determine Blood Pressure 374
Factors Affecting Blood Pressure 376
Diuretics 376
Drugs that Reduce Sympathetic Activity 379
Vasodilator Drugs 380



Leonello Calvetti/123RF

Drugs that Reduce the Activity of Angiotensin II 380
Treatment of Hypertensive Crisis 383
Patient Education and Monitoring 383
Preferred Therapy for Treatment of Hypertension 383
Chapter Review 385

CHAPTER 27

Anticoagulants and Coagulants 388

Blood Clot Formation 389
Anticoagulant Mechanisms of Action 391
Characteristics of the Heparins 392
Oral Anticoagulants 394
Antiplatelet Drugs 398
Special Considerations, Contraindications and Drug Interactions with Anticoagulants 399
Fibrinolytic/Thrombolytic Drugs 403
Clinical Uses of Coagulants/Hemostatics 404
Chapter Review 406

CHAPTER 28

Nutrition and Therapy 409

Nutrients and U.S. Daily Allowance Recommendations 410
Dietary Recommendations 411
Functions of Vitamins 415
Fat-Soluble Vitamins A, D, E, K 415
Water-Soluble Vitamins B and C 419
Body Water and Fluid Balance 421
Minerals 422
Intravenous Therapy 425
Chapter Review 427

CHAPTER 29

Hypolipidemic Drugs 431

Atherosclerosis and Arterial Disease 433
Lipids, Lipoproteins, and Cholesterol 433
Classes of Hypolipidemic Drugs 437
HMG-CoA Reductase Inhibitors: Statins 437
Cholesterol Absorption Inhibitors: Ezetimibe 441
Bile Acid Sequestrants: Cholestyramine, Colestipol, and Colesevelam 443
Other Hypolipidemic Drugs 443
Contraindications and Drug Interactions 445
Chapter Review 448

CHAPTER 30

Hematinics 451

- Anemia and Red Blood Cell Function 452
- Iron Deficiency Anemia 453
- Treatment of Iron Deficiency: Hematinics 455
- Cobalamin Deficiency Anemia 457
- Folic Acid Deficiency 459
- Erythropoietin Deficiency Anemia 461
- *Chapter Review 463*

PART 6

Drugs That Affect the Respiratory System 467

CHAPTER 31

Antihistamines and Mast Cell Stabilizers 468

- Allergy: The Role of Histamine 469
- Effects of Histamine 470
- Antihistamine H_1 Antagonists 472
- Mast Cell Stabilizers 478
- *Chapter Review 482*

CHAPTER 32

Respiratory Pharmacology, Treatment of Asthma and COPD 485

- Respiratory Diseases 486
- Chemical Mediators 488
- Role of the Autonomic Nervous System 489
- Bronchodilator Drugs 489
- Anti-inflammatory Drugs 493
- Antiallergic Agents 495
- Mucolytics and Expectorants 495
- Preferred Therapy for Asthma and COPD 496
- *Chapter Review 497*

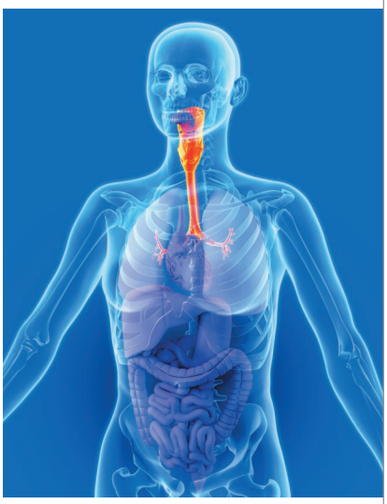
PART 7

Pharmacology of the GI Tract 501

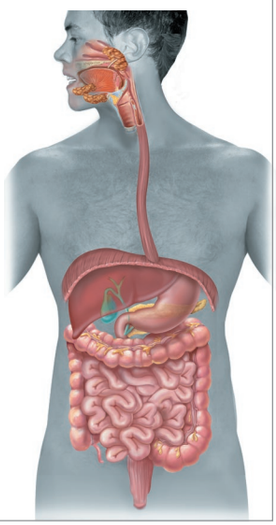
CHAPTER 33

Therapy of GI Disorders: Peptic Ulcers, GERD, and Vomiting 502

- Process of Digestion 503
- Peptic Ulcer and GERD 505



Roger Harris/Science Source



Management of GI Disorders 506
Antisecretory Drugs: Suppression of Gastric Acid 509
Acid Neutralization: Antacids 515
Barrier Enhancers: Sucralfate 518
Prokinetic Drugs for the Management of GERD 518
Management of Emesis 519
Drugs That Inhibit Vomiting: Antiemetics 520
Chapter Review 526

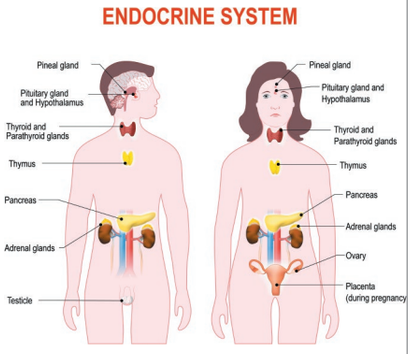
CHAPTER 34
Agents That Affect Intestinal Motility 529
Bowel Function 531
Diarrhea 531
Treatment of Simple Diarrhea 533
Causes of Constipation 535
Types of Laxatives Used in the Management of Constipation 536
Chapter Review 541

PART 8
Pharmacology of the Endocrine System 545

CHAPTER 35
Introduction to the Endocrine System 546
Basic Hormone Function 547
Hypothalamic-Pituitary Axis 549
Regulating Hormone Secretion 550
Endocrine Functions of the Anterior Pituitary Gland 551
Chapter Review 554

CHAPTER 36
Adrenal Steroids 557
Regulation of Adrenocorticoid Hormones 558
Primary Function of the Glucocorticoids 560
Clinical Uses of Glucocorticoids 561
Function of Mineralocorticoid Aldosterone 567
Special Cautions and Drug Interactions 569
Chapter Review 572

CHAPTER 37
Gonadal Hormones, Oral Contraceptives, and Erectile Dysfunction Drugs 575
Female Sex Hormones 577
Clinical Uses of Estrogen and Progestins 578



Designua/Shutterstock

Contraception: Oral Contraceptives and Hormone Delivery Systems 580
Hormonal Replacement Therapy 585
Other Clinical Uses of Estrogens and Progestogens 587
Fertility Drugs 588
Male Sex Hormones 590
Erectile Dysfunction 595
Chapter Review 598

CHAPTER 38

Drugs Affecting the Thyroid and Parathyroid Glands and Bone Degeneration 601
Function and Regulation of the Thyroid Gland 602
Effects of Thyroid Hormone Hyposecretion 604
Thyroid Hormone Replacement Therapy for Hypothyroidism 605
Effects of Thyroid Hormone Hypersecretion 607
Drugs Used to Treat Hyperthyroidism 608
Parathyroid Hormones: Role of Parathormone 610
Degenerative Bone Disease: Osteoporosis 613
Drugs Used for Bone Disorders 614
Chapter Review 617

CHAPTER 39

Pancreatic Hormones and Antidiabetic Drugs 620
Pancreatic Endocrine Function 622
Diabetes Mellitus 625
Treatment of Diabetes 627
Antidiabetic Drugs: Insulins 628
Parenteral Antidiabetic Drugs: Amylin Analog and Incretin Mimetics 636
Oral Antidiabetic Drugs: Secretagogues, Hypoglycemics 638
Other Oral Antihyperglycemic Drugs 642
Chapter Review 649

CHAPTER 40

Posterior Pituitary Hormones: Antidiuretic Hormone and Oxytocin 653
Posterior Pituitary Hormones 654
Antidiuretic Hormone 654
Diabetes Insipidus 656
Function and Clinical Use of Oxytocin 657
Tocolytics 658
Chapter Review 661

PART 9

Pharmacology of Infectious Diseases 665

CHAPTER 41

Antibacterial Agents 666

- Morphology of Bacteria 667
- Chemotherapy 668
- Penicillins 670
- Cephalosporins 673
- Aminoglycosides 675
- Tetracyclines 676
- Sulfonamides 677
- Macrolide Antibiotics 678
- Fluoroquinolone Antimicrobials 679
- Miscellaneous Antimicrobial Drugs 680
- Drugs Used to Treat Tuberculosis 681
- Preferred Therapy for Selected Infections 682
- *Chapter Review 684*

CHAPTER 42

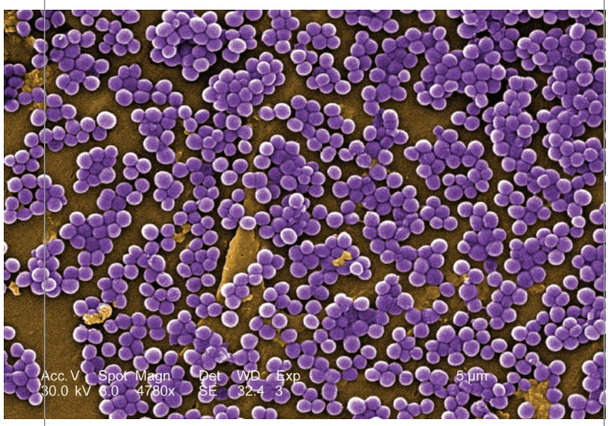
Antifungal and Antiviral Drugs 687

- Fungal Infections 689
- Antifungal Drugs 690
- Systemic Antifungal Drugs 693
- Oral and Topical Antifungal Drugs 697
- Viral Diseases 698
- Antiviral Drugs 705
- Mechanisms of Action 708
- Characteristics of Antiviral Drugs 713
- *Chapter Review 718*

CHAPTER 43

Parasitic Infections: Antiprotozoal and Anthelmintic Drugs 721

- Parasitic Infections: Protozoa and Worms 722
- Drugs Effective in the Treatment of Malaria (Antimalarial Drugs) 724
- Drugs Effective in the Treatment of Dysentery 726
- Other Protozoal Infections and Drug Treatment 728
- Drug Treatment of Parasitic Worm Infestations 730
- *Chapter Review 734*



Source: Janice Carr/CDC

CHAPTER 44

Antiseptics and Disinfectants 737

The Role of Antiseptics and Disinfectants 738

Categories of Antisepsis and Disinfection 739

Clinical Uses of Antiseptics and Disinfectants 743

Common Chemicals That Inhibit Infectious Microorganisms 743

Adverse Effects and Special Cautions 747

Chapter Review 748

PART 10

Antineoplastics and Drugs Affecting the Immune System 753

CHAPTER 45

Antineoplastic Agents and Oncology Immunotherapy 754

Types of Cancer 755

Alkylating Drugs 757

Antimetabolites 760

Drugs Derived from Natural Products 762

Hormone Antagonists 763

New Approaches to Cancer Chemotherapy 766

Chapter Review 768

CHAPTER 46

Immunopharmacology 771

Immune System 772

Immunosuppressive Drugs 774

Immunomodulating Drugs 777

Biosimilars 780

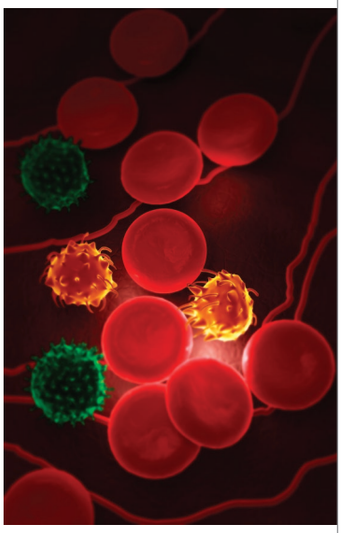
Chapter Review 782

Glossary 785

Appendix A: Latin Abbreviations Used in Medicine 800

Appendix B: Abbreviations and Symbols Commonly Used in Medical Notations 801

Index 805



MedicalRF.com/Getty Images

About the Authors

Don Wilkie/ E+/Getty Images

Henry Hitner earned a bachelor of science degree in biology from Moravian College in Bethlehem, Pennsylvania, and spent several years working in the pharmaceutical industry, first as a research assistant in toxicology for Wyeth Laboratories and then as a research pharmacologist for National Drug Company, both in Philadelphia. During this time he earned a master of education degree in biology from West Chester University. He attended graduate school at Hahnemann Medical College in Philadelphia, where he earned a PhD in pharmacology. Dr. Hitner then went into academia, where he held numerous faculty positions, first as an instructor of biology and allied health sciences at Montgomery County Community College, followed by 30 years of teaching and research at the Philadelphia College of Osteopathic Medicine (PCOM). At PCOM he served as professor and vice chair of the neuroscience, physiology, and pharmacology department. Other positions included director of the animal facility and chair of the institutional animal care and utilization committee. Professional memberships included the Sigma Xi Scientific Research Society and the American Society for Pharmacology and Experimental Therapeutics. He was the recipient of the Lindback Foundation Award for Distinguished Teaching and a Mentor Award from the National Student Association. Henry and his wife Carlotta enjoy traveling, the beach, and time spent with family and their nine grandchildren.

Barbara Nagle earned a master of science and doctorate at Hahnemann Medical College and University in the department of pharmacology. Following postdoctoral training in ocular pharmacology at Will's Eye Hospital, Philadelphia, she taught pharmacology and physiology to medical students at the Philadelphia College of Osteopathic Medicine (PCOM) and to nursing students at Widener University. After several years in academia, she moved into the pharmaceutical industry at Glaxo Smith-Kline, Endo Pharmaceuticals, Bio-Pharm Clinical Services, ICON, and InKine Pharmaceuticals, Inc. as Director of Clinical Information and later Vice President of Clinical Research, Training and Quality Assurance. She has been part of the research effort to bring products through clinical development to FDA approval such as gastric acid suppressants (antihistamines), beta-blockers, antiinfectives, muscle relaxants, and oral contraceptives. Her most recent affiliation was with Endo Pharmaceuticals in pain management research prior to her current activities as consultant and educator. She has served as International Director of Drug Development Training and Medical Education for BioPharm. Professional memberships include the Sigma Xi Scientific Research and American Medical Writers Association. Barbara is a freelance photographer, traveler, and silk painter.

Michele B. Kaufman, a pharmacist at NewYork-Presbyterian Hospital Lower Manhattan is also a board-certified geriatric and registered pharmacist. She has over 30 years of pharmacy experience, and earned her bachelor of science in pharmacy from the University of Rhode Island (URI) College of Pharmacy, Kingston. She has worked as a product development pharmacist in New Jersey and as a hospital pharmacist at Robert Wood Johnson University Hospital in New Brunswick, before returning to New England (Boston) to obtain a doctor of pharmacy degree at Massachusetts College of Pharmacy/AHS.

(Boston) Subsequently, she completed a fellowship in drug information (DI) at the URI DI Center/RWMC in Providence. Dr. Kaufman then became a clinical assistant professor at St. John's University, Jamaica, New York, specializing in DI/adult medicine (clinical site @ LIJMC). After several years in academia she became a geriatric clinical pharmacist in corporate managed care, where she stayed for over a decade. She then left to pursue medical writing and health-system pharmacy practice. She is an active member of professional organizations, including American Society of Health-System Pharmacists, Academy of Managed Care Pharmacy, American Medical Writers Association, American Society of Consultant Pharmacists, New York State Council of Health-System Pharmacists, New York City Society of Health-System Pharmacists (NYCSHP), and SWINY. She is a member of the clinical care committee at Callen-Lorde Community Health Center (NYC). She has mentored numerous students throughout her years, and coauthored and published her first book (2019), a health careers book for middle-grade ages and up, *Healthcare Heroes: The Medical Careers Guide*. She is the past recipient of two prestigious awards from NYCSHP, the Harold Neham Award (2006) for dedication and commitment to pharmacy practice and literature; and the Joel Yellin Award (2011), honoring significant pharmacy practice contribution. When not working, Michele enjoys traveling, spending time with family and friends, exploring new cultures, and playing musical instruments, mostly the saxophone.

Hannah (Cooke) Ariel received her doctor of pharmacy degree from the University of Michigan, Ann Arbor. She was recruited by the Harvard Affiliated Hospital, Beth Israel Deaconess Medical Center, serving as a clinical pharmacist in cardiology and general medicine, with an adjunct appointment at Harvard Medical School as a clinical assistant professor, and a full-time pharmacy practice appointment as associate professor of pharmacy practice at Massachusetts College of Pharmacy in Boston. Hannah met and married Moshe Ariel of Brookline, and together they are raising their four children—Sarah, Aharon, Ariyeh, and Tova Anna—in Saddle Rock, Long Island, New York. Hannah has a great love for her family, in addition to her passion for science and medicine. Hannah is a licensed pharmacist in New York, Massachusetts, and Florida, and currently holds an adjunct faculty appointment in chemistry and biochemistry at Queens College, Queens, New York.

Yael Peimani-Lalehzarzadeh earned her doctor of pharmacy degree from The Arnold & Marie Schwartz College of Pharmacy and Health Sciences at Long Island University, Brooklyn, New York, where she graduated with honors. She was president of the American Society of Consultant Pharmacists (ASCP), LIU Brooklyn Chapter during the fall of 2014. Dr. Lalehzarzadeh has experience in both retail pharmacy and consulting for nursing homes. She is a devoted wife and mother, and cherishes every moment with her family.

pixhook/Getty Images

Preface

The eighth edition of *Pharmacology: An Introduction* has been thoroughly updated, but the aim of this program remains what it has always been: to present a clear understanding of the basic concepts of pharmacology to the beginning student. Pharmacology is a complex subject that requires basic knowledge in many different scientific disciplines, particularly anatomy, physiology, and pathology. Health profession students often have limited exposure to these subjects, and one of the objectives of our text is to provide the necessary background information and to refresh the students' memory of previously learned material through which the therapeutic action of drugs can be clearly understood.

The goal of this text is to explain the **mechanisms of drug actions**. Understanding how drugs produce their effects allows the student to better understand the different pharmacologic actions and adverse effects that drugs produce. *Pharmacology: An Introduction* is designed for a variety of health profession programs requiring an understanding of pharmacology. The book presents a basic rationale for understanding current drug therapy. The drug information and chapter features are designed to be applicable and adaptable to many different educational programs. Personnel in the health and nursing professions spend much of their working time in direct contact with patients—observing, treating, and administering to the countless requirements and demands that constitute effective and responsible patient care. Therefore, it is important that students in health professions acquire a sound basic understanding of pharmacology as it relates to their particular needs.

New scientific discoveries and advances in the understanding of disease provide a continual introduction and approval of new drugs. At the same time, older drug therapies and drugs that cause serious adverse effects or other problems are eliminated. New advances in genetics and molecular biology have allowed the development of monoclonal antibodies and drugs with more selective mechanisms of action. These new agents can target specific receptors and physiologic functions that more accurately focus on the pathology of a particular disease process. Thus pharmacology is an ever-changing, growing body of knowledge that continually demands greater amounts of time and education from those in the health professions.

Organization

Pharmacology: An Introduction is organized into **10 sections.** The introductory section, *General Concepts,* presents the basic concepts and pharmacologic principles that apply to all drugs. Subsequent sections present the drug classes that pertain to a specific body organ system (nervous, cardiovascular, respiratory, etc.) or therapeutic indication (antihypertensives, infectious diseases, antineoplastics, etc.). The discussion of each drug classification concentrates on the mechanisms of action, main therapeutic effects, clinical indications, adverse reactions, and drug interactions.

Features

Pharmacology: An Introduction's hallmark features include:

- Readability: Short readable chapters that link theory to practice.
- Need-to-Know Information: The content is focused on need-to-know information, so not to overload the learner.
- Patient Administration and Monitoring Boxes: These features provide the student with critical patient information and patient instructions regarding the drugs discussed in the chapter.

Other key features:

- **Learning Outcomes** (LOs) have been completely revised in this edition. As always, the LOs are correlated to the Revised Bloom's Taxonomy and are numbered at the beginning of each chapter. LOs are linked to the main chapter topic headings, the end-of-chapter review questions, exam questions, instructor resources, and all content in Connect. This allows the student to more quickly associate the LOs with the location of that information in the text and with the answers to the review questions.
- ***Notes to the Health-Care Professional*** emphasize important points and information for medical personnel involved in drug administration.
- **Chapter reviews** at the end of each chapter progress from simple to complex and provide immediate reinforcement of terminology and pharmacologic concepts important for acquiring knowledge. The clinically relevant on-the-job questions allow students more opportunity to practice critical-thinking skills.

What's New?

- Revision and numbering of all learning outcomes to reflect the Revised Bloom's Taxonomy guide the student on a clear path to mastering chapter content.

- Updated chapter names to more closely correlate with newer medical terminology.
- New drug classes listed for high cholesterol, blood pressure, migraine, heart failure, blood thinning, nausea and vomiting, osteoporosis, cancer, infectious diseases, autoimmune diseases, and Alzheimer's disease.
- Updated tables with new drugs, new drug classes, and removal of drugs no longer used.
- Updated table of new combination HIV drugs.
- Updated section on the opioid crisis and treatments for opioid use disorder (OUD).
- Updated sections on box warnings, risk evaluation and mitigation strategies (REMS), and information on cannabidiol (CBD).

Epocrates Rx Drugs, by Epocrates Medical Information 2020

- Correlation of learning outcomes to all major chapter headings and end-of-chapter review questions will help the student and instructor focus on key chapter content.
- Revised tables organize and summarize the main pharmacologic features of the different drug classes. **Most often the tables list the generic drug name first followed by the trade name(s), which are italicized and put within parentheses.** These drug tables are particularly useful for students in health information management programs.

Updated drug information has been found by using several key sources:

- US Federal Drug Administration (FDA) provides daily updates on drug approvals, drug safety issues, medication guides, and drug industry information.
- FDA database on drug approvals and discontinuations is used to check status of market availability of branded and generic drugs.
- *www.centerwatch.com* is a leading source of information about the clinical trials (pharmaceutical drugs and devices) industry since 1994.
- *www.factsandcomparisons.com* by Wolters Kluwer is a searchable database by drug name or therapeutic category for all FDA-approved drugs (by paid subscription).
- Lexicomp by Wolters Kluwer is a searchable drug information database (by paid subscription).
- National Library of Medicine and National Institutes of Health Medical provide information on conditions, diseases, wellness, over-the-counter (OTC) and prescription medication at different levels to facilitate understanding by professionals, students, patients, and consumers.
- WebMD Health Professional Network provides evidence-based content, updated regularly by more than 8000 attributed physician or health-care provider authors and editors, and the latest practice guidelines in 38 clinical areas.
- Aetna *InteliHealth* provides credible information from trusted sources, including Harvard Medical School and Columbia University College of Dental Medicine.
- Professional Organizations are dedicated to providing accurate information to patients and health-care providers on a specific disease or condition.

In addition to providing innovative approaches to learning pharmacology, McGraw Hill Education knows how much effort it takes to prepare for a new course. Through focus groups, symposia, reviews, and conversations with instructors like you, we have gathered information about the materials you need in order to facilitate successful courses. We are committed to providing you with high-quality, accurate instructor support.

Additional Instructor Resources

- **Instructor's Manual** with course overview, lesson plans, answers for end-of-chapter exercises, competency correlations, Asset maps, and more.
- **PowerPoint Presentations** for each chapter, containing teaching notes correlated to learning outcomes. Each presentation seeks to reinforce key concepts and provide an additional visual aid for students.
- **Test Bank** and answer key for use in class assessment. The comprehensive test bank includes a variety of question types, with each question linked directly to a learning outcome from the text. Questions are also tagged with relevant topic, Bloom's Taxonomy level, difficulty level, and competencies. The test bank is available in Connect. Word and EZ Test versions are also available.

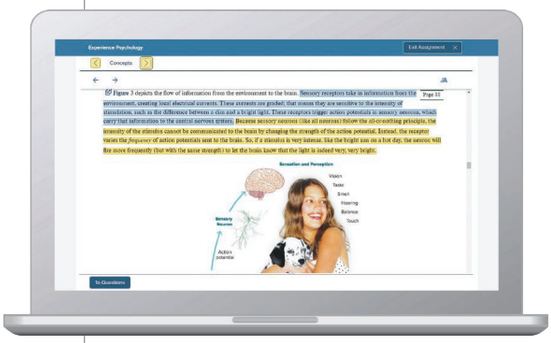
Mc Graw Hill connect®

Instructors: Student Success Starts with You

Tools to enhance your unique voice

Want to build your own course? No problem. Prefer to use our turnkey, prebuilt course? Easy. Want to make changes throughout the semester? Sure. And you'll save time with Connect's auto-grading too.

65%
Less Time Grading



Laptop: McGraw Hill; Woman/dog: George Doyle/Getty Images

Study made personal

Incorporate adaptive study resources like SmartBook® 2.0 into your course and help your students be better prepared in less time. Learn more about the powerful personalized learning experience available in SmartBook 2.0 at **www.mheducation.com/highered/connect/smartbook**

Affordable solutions, added value

Make technology work for you with LMS integration for single sign-on access, mobile access to the digital textbook, and reports to quickly show you how each of your students is doing. And with our Inclusive Access program you can provide all these tools at a discount to your students. Ask your McGraw Hill representative for more information.

Padlock: Jobalou/Getty Images

Solutions for your challenges

A product isn't a solution. Real solutions are affordable, reliable, and come with training and ongoing support when you need it and how you want it. Visit **www.supportateverystep.com** for videos and resources both you and your students can use throughout the semester.

Checkmark: Jobalou/Getty Images

SUPPORT AT every step

Students: Get Learning that Fits You

Effective tools for efficient studying

Connect is designed to make you more productive with simple, flexible, intuitive tools that maximize your study time and meet your individual learning needs. Get learning that works for you with Connect.

Study anytime, anywhere

Download the free ReadAnywhere app and access your online eBook or SmartBook 2.0 assignments when it's convenient, even if you're offline. And since the app automatically syncs with your eBook and SmartBook 2.0 assignments in Connect, all of your work is available every time you open it. Find out more at **www.mheducation.com/readanywhere**

"I really liked this app—it made it easy to study when you don't have your text-book in front of you."

- Jordan Cunningham, Eastern Washington University

Calendar: owattaphotos/Getty Images

Everything you need in one place

Your Connect course has everything you need—whether reading on your digital eBook or completing assignments for class, Connect makes it easy to get your work done.

Learning for everyone

McGraw Hill works directly with Accessibility Services Departments and faculty to meet the learning needs of all students. Please contact your Accessibility Services Office and ask them to email accessibility@mheducation.com, or visit **www.mheducation.com/about/accessibility** for more information.

Top: Jenner Images/Getty Images, Left: Hero Images/Getty Images, Right: Hero Images/Getty Images

Remote Proctoring & Browser-Locking Capabilities

New remote proctoring and browser-locking capabilities, hosted by Proctorio within Connect, provide control of the assessment environment by enabling security options and verifying the identity of the student.

Seamlessly integrated within Connect, these services allow instructors to control students' assessment experience by restricting browser activity, recording students' activity, and verifying students are doing their own work.

Instant and detailed reporting gives instructors an at-a-glance view of potential academic integrity concerns, thereby avoiding personal bias and supporting evidence-based claims.

Acknowledgments

A sincere thanks to our reviewers and contributors who helped shape the development of the eighth edition.

Reviews

Terri Blevins
Tennessee College of Applied Technology

Lisa Blackburn
Tennessee College-Applied Technology Elizabethton

Denise M. Brehmer
Indiana Wesleyan University

Kristy Carlisle
Southwest Mississippi Community College

Jennifer Dietz
Cuyahoga Community College

Patricia Dominguez
Houston Baptist University

Nelda Fister
University of Central Oklahoma

Tim Gilmore
Louisiana State University Health Sciences Center, Shreveport

Cristal M. Greene
Hutchinson Community College

Amber Greer
Nash Community College

Veronica Jackson
Wallace Community College Selma

Amie Lund
University of North Texas

Diane McLean
Coastal Alabama Community College

Kristina Perkins
Chabot College

Beth Roraback
Greenville Technical College

Teresa Seefeldt
South Dakota State University and Allied Health Professions

Michele Shuman
Gwynedd Mercy University

Kathy Smith
University of Central Oklahoma

Karen Snipe
Trident Technical College

Elizabeth A. VandeWaa
University of South Alabama

Cheryl Vineyard
Eastern New Mexico University–Roswell

Amy Voytek
Westmoreland County Community College

Sandra Wilson
Crowder College

Nicholas Zaksek
Westmoreland County Community College

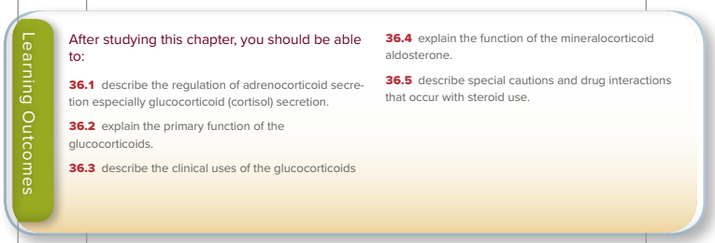
What Every Student Needs to Know

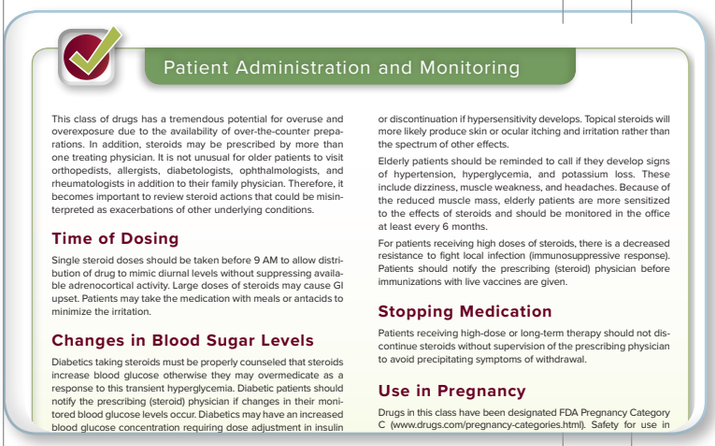
Many tools to help you learn have been integrated into *Pharmacology: An Introduction*.

Chapter Features

Learning Outcomes

present the key points you should focus on when reading the chapter. Consider this your road map to the knowledge and skills you will acquire upon studying this content.





Patient Administration and Monitoring boxes

summarize important patient information and patient instructions about the drugs discussed in that chapter. It will expand your knowledge of medications and conditions.

Notes to the Health-Care Professional

emphasizes important points and information for medical personnel involved in drug administration.

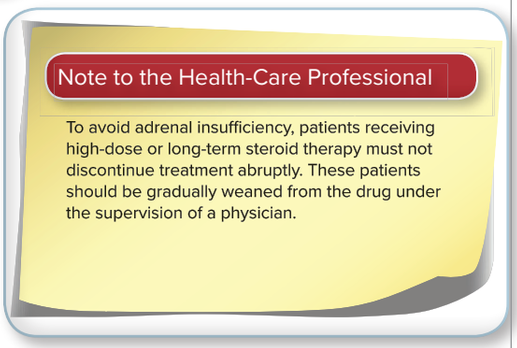


Table 36.6

Examples of Drug Interactions Associated with Glucocorticoids

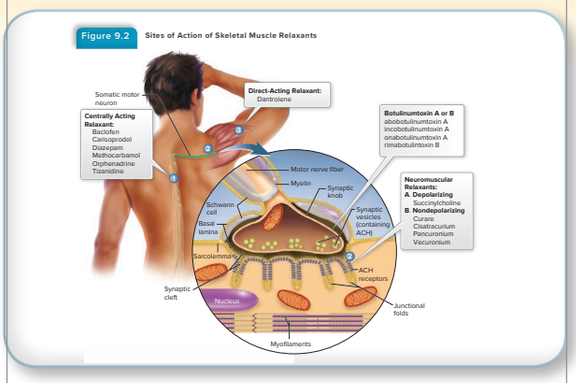
Glucocorticoids interact with	Response
Amphotericin B, digitalis, diuretics	Potentiate hypokalemia (possible digitalis toxicity)
Antibiotics, macrolide	Increase methylprednisolone clearance from plasma
Aspirin	Increase GI side effects by an additive effect
Growth hormone	Decrease growth-promoting effect of growth hormone
Insulin, oral hypoglycemics	Increase requirement for insulin or oral hypoglycemics
Isoniazid	Increase requirements for isoniazid
Oral contraceptives, estrogens, ketoconazole	Increase response of glucocorticoid and mineralocorticoid because of decreased steroid metabolism

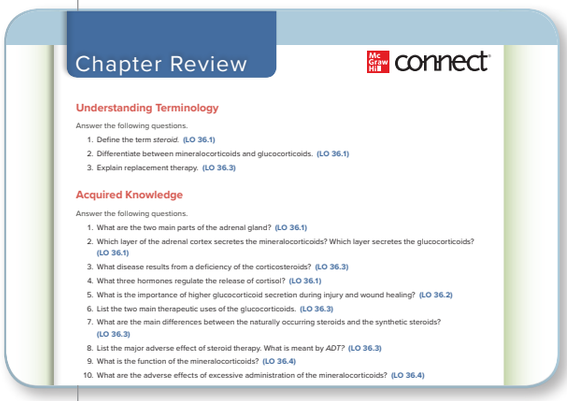
Drug Tables

organize and summarize the main pharmacologic features of the different drug classes. The tables most often list the generic drug name first followed by the trade name(s), which are italicized and put within parentheses.

Illustrations and Photos

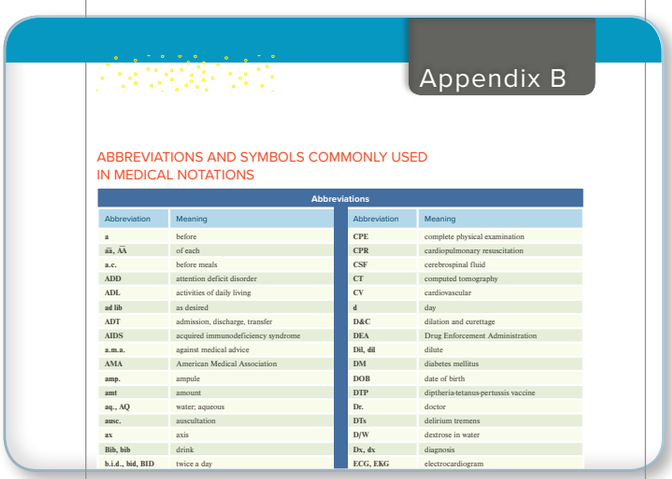
provide a dynamic visual picture of the action of drugs and drug products to help you understand pharmacologic processes that are discussed in the text. Illustrations provide just the right level of detail to help explain the processes described.





Chapter Reviews

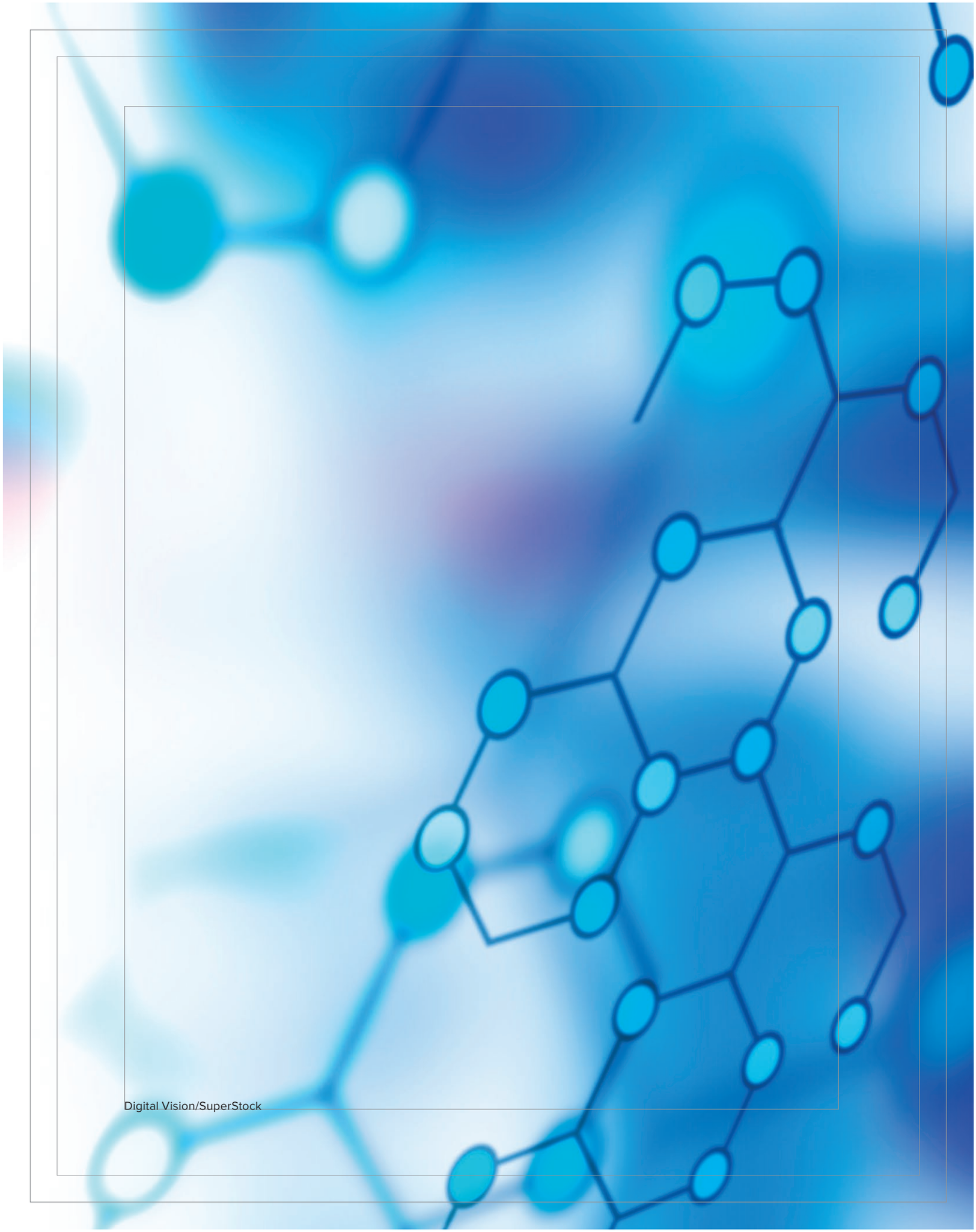
provide immediate reinforcement of terminology and pharmacological concepts important for acquiring knowledge. These questions, which are also available in Connect, challenge you to apply information presented in the chapter. The clinically relevant on-the-job questions allow you more opportunity to practice critical-thinking skills.



Appendices

provide additional information pertinent to the study of pharmacology. You will find lists of abbreviations and symbols used in medical notations, weights and measures, and mathematical functions and terms.

Levent Ince/Getty Images



Digital Vision/SuperStock

PART 1

General Concepts

CHAPTER 1

Pharmacology: An Introduction 4

CHAPTER 2

Pharmacokinetics and Factors of Individual Variation 17

CHAPTER 3

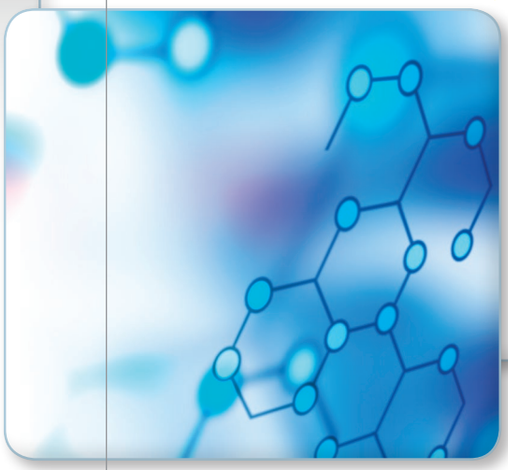
Geriatric Pharmacology 34

CHAPTER 4

Math Review and Dosage Calculations 43

snappphoto/Getty Images

Chapter 1



Jason Reed/Getty Images

Pharmacology: An Introduction

KEY TERMS

adverse effect: general term for undesirable and potentially harmful drug effect.

agonist: drug that binds to a receptor and activates a physiologic response or drug action.

antagonist: drug that binds to a receptor and interferes with other drugs or substances from producing a drug effect.

chemical name: name that defines the chemical composition of a drug.

contraindications: situations or conditions when a certain drug should not be administered.

controlled substance: drug that has the potential for abuse and thus is regulated by law.

dose: a measurement of the amount of drug that is administered.

drug: chemical substance that produces a change in body function.

drug indications: intended or indicated uses for any drug.

ED50: effective dose 50, or dose that will produce an effect that is half of the maximal response.

generic name: nonproprietary name of a drug.

LD50: lethal dose 50, or dose that will kill 50 percent of the laboratory animals tested.

mechanism of action: explanation of how a drug produces its effects.

nonprescription, over-the-counter (OTC) drug: drug that can be purchased without the services of a physician.

pharmacology: study of drugs.

potency: measure of the strength, or concentration, of a drug required to produce a specific effect.

prescription drug: drug for which dispensing requires a written or phone order that can only be issued by or under the direction of a licensed physician.

receptor: specific cellular structure that a drug binds to in order to produce a physiologic effect.

side effect: drug effect other than the therapeutic effect that is usually undesirable but not harmful.

site of action: location within the body where a drug exerts its therapeutic effect, often a specific drug receptor.

therapeutic effect: desired drug effect to alleviate some condition or symptom of disease.

therapeutic index (TI): ratio of the LD50 to the ED50 in animal studies.

toxic effect: undesirable drug effect that implies drug poisoning; can be very harmful or life-threatening.

trade name: patented proprietary name of a drug sold by a specific drug manufacturer; also referred to as the brand name.

Learning Outcomes

After studying this chapter, you should be able to:

1.1 list and define the major areas of pharmacology.

1.2 describe what a drug is and explain the differences between therapeutic effect, side effect, and toxic effect.

1.3 understand the terms **site of action** and **mechanism of action**, and how agonist and antagonist drugs interact at drug receptor sites.

1.4 characterize the relationship between drug dosage and drug response, and the relationship between drug response and time.

1.5 understand the terms associated with drug safety: *therapeutic index, idiosyncrasy, drug allergy,* and *teratogen*.

1.6 explain the nomenclature used to name and classify drugs.

1.7 recall the main drug references and the information they provide.

Introduction

Pharmacology is the study of drugs. A drug can be any substance that, when administered to living organisms, produces a change in function. Thus, substances such as water, metals (iron), or insecticides can be classified as drugs. However, the term *drug* commonly refers to any medication that is used for diagnosing, curing, or treating disease.

Pharmacology is a subject that requires some background knowledge of anatomy, physiology, pathology, and related medical sciences. In that sense pharmacology is an integrative course of study that applies the relevant information of all medical sciences to the treatment of disease. Throughout this textbook the essential background information of anatomy, physiology, and pathology required for an understanding of drug action will be reviewed. The major focus of *Pharmacology: An Introduction* is to provide an understanding of the mechanisms of action, main therapeutic effects, clinical uses, and adverse reactions of drugs. Completion of an introductory pharmacology course is only the beginning step in understanding this complex subject.

LO 1.1

DRUG SOURCES AND MAJOR AREAS OF PHARMACOLOGY

Drug Sources

A logical question to ask about pharmacology is, "Where do drugs come from?" There are several sources of drugs. In the early days of medicine, most drugs were obtained from plant or animal sources. Plants and living organisms contain active substances that can be isolated, purified, and formulated into effective drug preparations. Examples of drugs derived from plants that are still widely used today include the analgesics morphine and codeine, which were obtained from the poppy plant (*Papver somniferum*); the heart drug digitalis, which was obtained from the purple foxglove (*Digitalis purpurea*); and the antimalarial drug quinine, which was obtained from the bark of the cinchona tree. Paclitaxel, an anticancer drug, is obtained from the yew tree. The search for new plant drugs is still very active. It is also interesting that many of the drugs of abuse such as cocaine, marijuana, mescaline, heroin, and others are derived from plants. Most of these drugs were used for hundreds of years by many different cultures in their religious and ritual ceremonies. Drugs obtained from living organisms include hormones such as insulin (from the pig) and growth hormone from pituitary glands. In addition, antibiotics such as cephalosporins and aminoglycosides have been derived from bacteria. The early history of pharmacology is filled with many interesting stories of discovery and medical experimentation. Textbooks devoted to the history of medicine and pharmacology are the best sources for additional information. Despite the many examples of drugs obtained from plants and living organisms, the main

Table 1.1

Major Areas of Pharmacology

Area	Description
Pharmacodynamics	Study of the action of drugs on living tissue
Pharmacokinetics	Study of the processes of drug absorption, distribution, metabolism, and excretion
Pharmacotherapeutics	Study of the use of drugs in treating disease
Pharmacy	Science of preparing and dispensing medicines
Posology	Study of the amount of drug that is required to produce therapeutic effects
Toxicology	Study of the harmful effects of drugs on living tissue

source of new drugs today is from chemical synthesis. Also, many of the drugs that once were obtained from plants and animals are now chemically synthesized in pharmaceutical laboratories. Advances in molecular biology and gene therapy have generated new types of drugs such as monoclonal antibodies.

Pharmacology is a large discipline that can be subdivided into different areas of study. These include pharmacodynamics, pharmacokinetics, pharmacotherapeutics, pharmacy, posology, and toxicology. These areas of study are described in Table 1.1.

LO 1.2

TERMINOLOGY RELATED TO DRUG EFFECTS

Major Areas of Pharmacology

Another basic question that should be answered is, "What actually is a **drug**?" Every pure drug is a chemical compound with a specific chemical structure. Because of its structure, a drug has certain properties that are usually divided into chemical properties and biological properties. The properties of any drug determine what effects will be produced when the drug is administered. An important fact to remember is that, structurally, the human body is composed mostly of cells, even though these cells are highly organized into tissues, organs, and systems. Consequently, drugs produce effects by influencing the function of cells.

Pharmacologists know that all drugs produce more than one effect. Every drug produces its intended effect, or **therapeutic effect**, along with other effects. The therapeutic use(s) of any drug is referred to as the **drug indication**, meaning indications for use. The term **contraindication** refers to the situation or circumstance when a particular drug should *not* be used. Some drug effects, other than therapeutic effects, are described as undesirable. Undesired drug effects are categorized as side effects, adverse effects, and toxic effects.

Side Effects

Many **side effects** are more of a nuisance than they are harmful. The dry mouth and sedation caused by some antihistamine drugs is an example. In many cases drug side effects must be tolerated to benefit from the therapeutic actions of the drug.

Adverse Effects

Adverse effects are also undesired effects, but these are effects that may be harmful (persistent diarrhea, vomiting, or central nervous system [CNS] disturbances such as confusion) or that with prolonged treatment may cause conditions that affect the function of vital organs such as the liver or kidney. Reduction of dosage or switching to an alternative drug often will avoid or minimize these harmful consequences.

Toxic Effects

Toxic effects, or toxicity, implies drug poisoning, the consequences of which can be extremely harmful and may be life-threatening. In these situations, the drug must be stopped and supportive treatment and the administration of antidotes may be required.

The term most frequently used to describe the undesirable effects of drugs is *adverse effects.* However, you should be familiar with the other terms because they are used and, if used correctly, describe the nature and potential severity of undesired drug effects.

Most drugs will cause all three types of undesired effects, depending on the dose administered. At low doses, side effects are common and often expected. At higher doses, additional adverse effects may appear. At very high doses, toxic effects may occur that can be fatal. Consequently, the undesired effects produced by most drugs are often a function of dosage, which is why a well-known physician from the Middle Ages, Paracelsus (1493–1541), made the famous statement, "Only the dose separates a drug from a poison"—and we could add, "a therapeutic effect from a toxic effect." Allied health personnel spend the majority of their time in patient contact. Therefore, they have an important responsibility to observe the undesired effects of drugs, to recognize the side effects that are often expected, and to identify and report the adverse and toxic effects that are potentially harmful and that often require medical attention.

LO 1.3

BASIC CONCEPTS IN PHARMACOLOGY

As in any subject, fundamental principles and concepts form the basis upon which additional information can be added. Pharmacology is no exception, and the following basic concepts apply to any drug.

Site of Action

The **site of action** of a drug is the location within the body where the drug exerts its therapeutic effect. The site of action of some drugs is not known; however, the site of action for most drugs has been determined. For example, the site of action of aspirin to reduce fever is in an area of the brain known as the hypothalamus. Within the hypothalamus the temperature-regulating center controls and maintains body temperature. Aspirin alters the activity of the hypothalamus so that body temperature is reduced. Throughout this book, when the site of drug action is known or suspected, it will be presented.

Mechanism of Action

Mechanism of action explains how a drug produces its effects. For example, local anesthetic agents produce a loss of pain sensation by interrupting nerve conduction in sensory nerves. For nerve impulses to be conducted, sodium ions must pass through the nerve membrane. Local anesthetic agents attach to the nerve membrane and prevent the passage of sodium ions. Consequently, sensory nerve impulses for pain are not conducted to the pain centers in the brain. Knowledge of the mechanism of action of drugs is essential to understanding why drugs produce the effects that they do.

Receptor Site

Drug action is usually thought to begin after a drug has attached itself to some chemical structure located on the outer cell membrane or within the cell itself. For a few drugs and for some normal body substances, there seems to be a specific location on certain cells. This area is referred to as the **receptor** site. The attachment, or binding, of a drug to its receptors begins a series of cell changes referred to as the drug action.

When a specific receptor site for a drug is known, that receptor site becomes the site of action for that particular drug. Morphine, an analgesic drug, is an example of a drug that binds to a specific receptor. The receptors for morphine are located in the brain and are known as the morphine, or opioid, receptors. When morphine binds to its receptors, it produces cell changes that reduce the perception of pain. There are many different pharmacologic receptors, and they will be described in the appropriate chapters.

Agonists and Antagonists

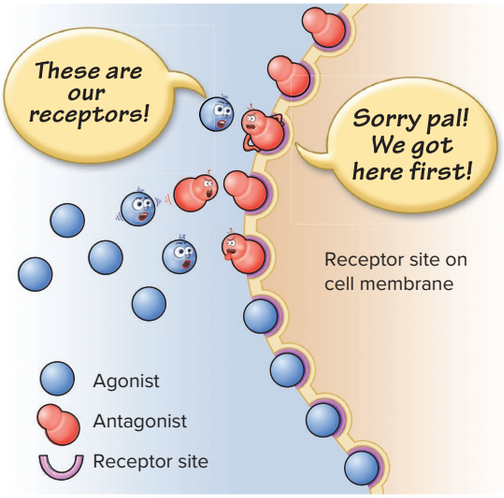
Drugs that bind to specific receptors and produce a drug action are called **agonists**. Morphine is an example of an agonist. Drugs that bind to specific receptors and block agonist drug action or cellular functions are called **antagonists**.

Antagonists are also known as blocking drugs. Usually, antagonists bind to a specific receptor to displace or prevent an agonist drug or body substance from activating that receptor. Naloxone, a morphine antagonist, is administered to prevent, or antagonize, the effects of morphine in cases of morphine overdose. There are many examples in pharmacology where drug antagonists are used to prevent other substances from exerting an effect.

When both agonist and antagonist drugs bind to the same receptor and are administered together, they compete with each other for the same receptor site. This effect is known as *competitive antagonism.* The amount of drug action produced depends on which drug (agonist or antagonist) occupies the greatest number of receptors. The actions of a drug agonist and antagonist are illustrated in Figure 1.1. There is also uncompetitive antagonism, which occurs when the antagonist drug interferes with the agonist drug action but not by binding to the same receptor.

Figure 1.1

Competitive Antagonism at Work



LO 1.4

DOSE-RESPONSE AND TIME-PLASMA DRUG CONCENTRATION CURVES

Dose-Response Curve

A fundamental principle of pharmacology is that the response to any drug depends on the amount of drug given. This principle is known as the dose-response relationship. A **dose** is the exact amount of a drug that is administered to produce a specific effect. The effect is referred to as the response. When the relationship between the dose and the response is plotted as a graph, it is referred to as a dose-response curve.

Figure 1.2 illustrates the appearance of a typical dose-response curve for two similar drugs. The main feature of the dose-response relationship is that a drug response is proportional to the dose. As the dose increases, so does the magnitude of the response. Eventually, a *maximal response* is usually attained (100 percent response); further increases in dose do not produce any greater effect. This point on the graph is known as the ceiling effect. The *ceiling effect* reflects the limit of some drug classes to produce a particular effect. Above a certain dosage no further increase in effect is observed. Doses above those needed to produce the ceiling effect usually cause other undesired, often toxic, drug effects. Drugs within a drug class that are more potent than other drugs in the same class will produce the ceiling effect at a lower dosage, but they will not "raise the ceiling." Drugs that continue to cause an increased effect as long as the dose is increased do not have a ceiling effect.

A graded dose-response curve can be used to evaluate drug response among different drugs. In a graded dose-response curve, the increases in drug dosage are plotted against the increases in drug response. For example, dose-response curves are used to compare the potency of similar drugs. **Potency** is a measure of the strength, or concentration, of a drug required to produce a specific effect. The dose that will produce an effect that is half of the maximal response is referred to as the effective dose 50, or **ED50**.

The ED50 can be used to compare the potency of drugs that produce the same response. In Figure 1.2, the ED50 of drug A is 10 mg while the ED50 of drug B is 20 mg. Therefore, drug A is twice as potent as drug B. Twice the concentration of drug B is needed to produce the same response as drug A.

Quantal (referred to as all-or-none) dose-response curves are used to show the percentage of a human or animal population that responds to a specific drug dosage. This information is important for determining the dosages that are recommended for various treatments. Quantal dose-response curves require an understanding of mathematical statistics that is beyond the scope of this textbook.

Time-Plasma Drug Concentration Curve

The relationship of time and the plasma drug concentration is known as the time-plasma drug concentration curve or time-response curve since it reflects the

Figure 1.2

A Typical Dose-Response Curve

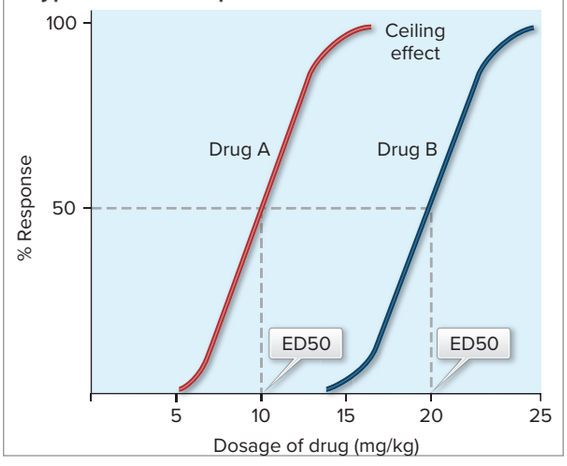
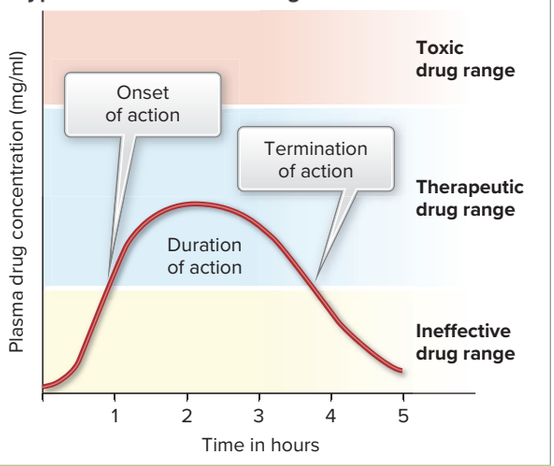


Figure 1.3

A Typical Time-Plasma Drug Concentration Curve



This curve shows the change in plasma drug concentration over time in relation to onset, duration, and termination of drug action. Plasma drug concentrations that exceed the therapeutic range produce drug toxicity.

duration of action. *Duration of action* is the length of time that a drug continues to produce its effect. Most individual drugs produce effects over a relatively constant period of time. Figure 1.3 illustrates the appearance of a typical time-plasma drug concentration curve. In this example, the plasma drug concentration is correlated with the onset, duration, and termination of drug action. After drug administration, a certain amount of time is required before a drug will produce an observable effect. The time from drug administration to the first observable effect is known as the *onset of action.* The drug response will continue as long as there is an effective concentration of the drug at the site of action. As the drug is metabolized and excreted, the response gradually decreases because the drug level is decreasing. When the plasma drug concentration falls below the therapeutic range, there is *termination of drug action.* Time-plasma drug concentration curves are used for predicting the frequency with which a drug must be administered in order to maintain an effective drug response.

LO 1.5

DRUG SAFETY

The federal Food and Drug Administration (FDA) has established guidelines that govern the approval and use of all drugs. Every drug must fulfill two major requirements before it can be approved for use in humans: efficacy (proof of effectiveness) and safety. The drug must be effective in the disease state for which it has been approved. Approved drugs must satisfy specific safety criteria as determined by extensive animal testing and controlled human testing. As discussed previously, the dose separates therapeutic effects from toxic effects.

Note to the Health-Care Professional

All drugs will act as poisons if taken in excess. Only the dose separates a therapeutic effect from a toxic effect. The goal of drug therapy is to select a dose that is in the therapeutic range and avoid doses that produce toxicity. This task is not easy because many factors influence the amount of drug that reaches its site of action. These factors—such as route of administration, absorption, and drug metabolism—will be discussed in Chapter 2.

Drug safety receives much attention today. It is a constant source of concern and debate because the public is more aware of the dangers of drugs. To receive approval for use in humans, a drug must undergo several years of both animal and human testing and evaluation. Several animal species must be used to evaluate the effectiveness and toxicity of a drug. One of the first tests that is performed is the lethal dose 50, or **LD50**. The LD50 is the dose that will kill 50 percent of the animals tested. The results of the LD50 and other tests are used to predict the safety of a drug.

Therapeutic Index

The **therapeutic index (TI)** is a ratio of the LD50 to the ED50 of a drug. It gives an estimate of the relative safety of a drug. The equation is expressed as:

$$TI = LD50/ED50 = 1000\ mg/100\ mg = 10$$

In this example, the therapeutic index is 10. This index indicates that 10 times as much drug is needed to produce a lethal effect in 50 percent of the animals as is needed to produce the therapeutic effect in 50 percent of the animals. The therapeutic index is used only in animal studies to establish dosage levels for other testing procedures. The goal of drug therapy is to achieve therapeutic effects in all individuals without producing any harmful effects.

Adverse Drug Effects

All drugs produce adverse and toxic effects if taken in excess. Most adverse effects are dose dependent, which means the higher the dose, the greater the chances for producing an adverse effect. Certain tissues are more frequently affected than others. Oral drugs often cause nausea, vomiting, and diarrhea because of gastrointestinal (GI) irritation. The liver, kidneys, brain, and cardiovascular system may be adversely affected because these organs are exposed to the highest concentrations of the drug. Drugs that produce birth defects, such as thalidomide, are known as *teratogens.* Drugs that promote the growth of cancerous tumors are called *carcinogens.*

A few adverse effects are not dose dependent. These effects, such as drug idiosyncrasy and drug allergy, are determined by individual variation. Although all human beings are basically similar, there may be minor variations in certain enzymes or other body proteins. These variations may produce changes in drug metabolism that lead to unusual responses to a particular drug. An individual reaction to a drug with an unusual or unexpected response is known as an *idiosyncrasy.*

Drug allergy occurs when an individual becomes sensitized to a particular drug (drug acts as an antigen) and produces antibodies against the drug. Subsequent administration of the drug leads to an antigen-antibody reaction. Antigen-antibody reactions involving drugs usually cause the release of histamine and other inflammatory mediators from cells known as mast cells. These inflammatory mediators produce the characteristic symptoms of allergy, which include rashes, hives, itching, nasal secretion, hypotension, and bronchoconstriction.

In serious allergic reactions, the symptoms may be so severe that death may occur. The term *anaphylaxis* is used to describe these serious allergic reactions, which include severe hypotension, respiratory difficulties, and cardiovascular collapse.

LO 1.6

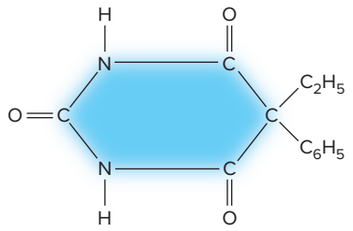
DRUG NOMENCLATURE

All drugs are chemicals, and many have long **chemical names**. As a result, all drugs are given a shorter name, known as the nonproprietary name, which is usually a contraction of the chemical name. The nonproprietary name is more commonly referred to as the **generic name**.

When the drug is marketed by a pharmaceutical company, it is given a third name, known as the proprietary name, or **trade name** or brand name. Since several different pharmaceutical companies may market the same generic drug, there may be several different trade names for any one drug. Figure 1.4 gives three names of a commonly prescribed drug.

Figure 1.4

Drug Nomenclature



Chemical name: 5,5,-Phenylethylbarbituric acid
Nonproprietary name: Phenobarbital (generic name)
Proprietary name: *Luminal, Solfoton* (trade or brand name)

Drugs are also divided into prescription and nonprescription drugs. **Prescription drugs** require a written or phone order (the prescription), which can only be issued by or under the direction of a licensed physician, dentist, or veterinarian. The prescription is a legal document that contains instructions for the pharmacist, who is licensed to dispense prescription medications. **Nonprescription drugs**, usually referred to as **"over-the-counter" (OTC) drugs** (such as aspirin, antacids, cold remedies), can be purchased anywhere and do not require the services of a physician or pharmacist. Otherwise, OTC drugs follow the same pharmacologic principles as prescription drugs. In this textbook, OTC drugs are included in the chapters where their use is indicated.

LO 1.7

DRUG REFERENCES AND DRUG LEGISLATION

Drug References

Medical libraries, hospital libraries, and educational institutions that provide medical education generally stock one or more drug reference books that provide drug information.

The United States Pharmacopeia/National Formulary (USP/NF) is the official drug list recognized by the U.S. government. It provides information concerning the physical and chemical properties of drugs. The *USP/NF* is revised every 5 years and is used primarily by drug manufacturers to ensure drug production according to official government standards.

Drug Facts and Comparisons (F&C) is a loose-leaf index and drug information service subscribed to by most medical libraries. Drug information and new drug additions are updated monthly. This index provides the most current drug information on a regular basis.

The United States Pharmacopeial Convention, Inc., publishes a series of volumes under the general title of *United States Pharmacopeia Dispensing Information* (USP DI) that are updated yearly. Volume I—*Drug Information for the Health Care Professional*—provides in-depth information about prescription and over-the-counter medications, and nutritional supplements. Volume II—*Advice for the Patient*—provides drug information for the patient.

Drug Information—American Hospital Formulary Service provides detailed drug information. Drugs are organized according to therapeutic use and classification. It is updated yearly.

Drug Legislation Acts

During the last century there was an increase in the discovery and introduction of new drugs. Correspondingly there was an increase in the reports of adverse drug effects and toxicities. Consequently, the government began to enact legislation aimed at ensuring the safety and effectiveness of drugs. The following is a brief summary of the major legislative acts.

1906: Federal Pure Food and Drug Act. This was the first real drug law that required drugs to have minimal standards of drug strength and purity. This law did not address the issue of drug efficacy or effectiveness. In 1912 the law was amended to include regulations for labeling and false claims of effectiveness.

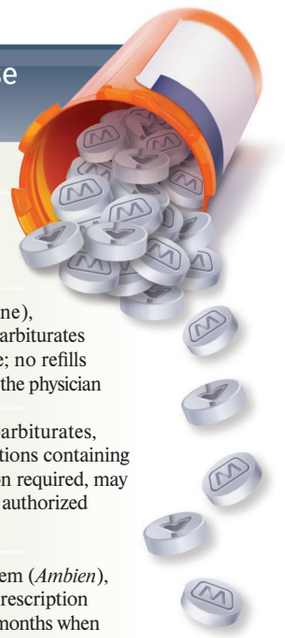
1938: Federal Food Drug and Cosmetic Act. This act set standards for drug safety and was enacted after 40 patients died from taking an antibiotic that contained diethylene glycol as a solvent. Drug manufacturers now had to show proof of drug safety.

1962: Amendment to 1938 Federal Food Drug and Cosmetic Act. In 1960 thalidomide, a hypnotic drug, was discovered to produce phocomelia, a rare birth defect that caused abnormal limb development. This act required pharmacologic and toxicologic research testing in several animal species before a drug could be tested in humans. The act also established the clinical requirements for human drug testing and, in addition, established the standards for both drug safety and effectiveness. This act is enforced by the Food and Drug Administration.

1970: Federal Comprehensive Drug Abuse Prevention and Control Act. This act, commonly referred to as the Controlled Substance Act, was amended in 1990. This act is designed to regulate the dispensing of drugs, called **controlled substances**, that have the potential for abuse. The controlled drugs are assigned to one of five schedules, depending on their medical usefulness and potential for abuse. This act is enforced by the Drug Enforcement Administration (DEA). Table 1.2 describes the schedules and provides examples of some controlled substances. Some U.S. states have recently legalized the use of marijuana; however, federal law still lists marijuana as a schedule I drug.

Table 1.2

Drug Schedules Defined in the Federal Comprehensive Drug Abuse Prevention and Control Act



Schedule	Definition	Controlled drugs
I	Drugs with high abuse potential and no accepted medical use	Heroin, hallucinogens, marijuana; these drugs are not to be prescribed
II	Drugs with high abuse potential and accepted medical use	Narcotics (morphine and pure codeine), cocaine, amphetamines, short-acting barbiturates (*Amobarbital, Secobarbital*), nabilone; no refills without a new written prescription from the physician
III	Drugs with moderate abuse potential and accepted medical use	Moderate- and intermediate-acting barbiturates, dronabinol, anabolic steroids, preparations containing codeine plus another drug; prescription required, may be refilled five times in 6 months when authorized by the physician
IV	Drugs with low abuse potential and accepted medical use	Phenobarbital, chloral hydrate, zolpidem (*Ambien*), antianxiety drugs (*Librium, Valium*); prescription required, may be refilled five times in 6 months when authorized by the physician
V	Drugs with limited abuse potential and accepted medical use	Narcotic drugs used in limited quantities for antitussive (codeine) and antidiarrheal purposes (diphenoxylate, *Lomotil*); drugs can be sold only by a registered pharmacist; buyer must be 18 years old and show identification. Some states require a prescription for this class of drugs

Chapter Review

Understanding Terminology

Match the definition in the left column with the appropriate term in the right column. **(LO 1.1)**

___ 1. The study of the amount of drug that is required to produce therapeutic effects.

___ 2. The study of the harmful effects of drugs on living tissue.

___ 3. The study of the action of drugs on living tissue.

___ 4. The study of drugs.

___ 5. The science of preparing and dispensing medicines.

___ 6. The study of the processes of drug absorption, distribution, metabolism, and excretion.

___ 7. The study of the use of drugs in treating disease.

a. pharmacodynamics
b. pharmacokinetics
c. pharmacology
d. pharmacotherapeutics
e. posology
f. pharmacy
g. toxicology

Answer the following questions.

8. Define a drug. **(LO 1.2)**
9. Differentiate between therapeutic effect, side effect, and toxic effect. **(LO 1.2)**
10. What is the difference between site of action and mechanism of action? **(LO 1.3)**
11. What is the relationship between ED50, LD50, and therapeutic index? **(LO 1.5)**
12. Explain the difference between a prescription drug, OTC drug, and a controlled substance. **(LO 1.6)**
13. Explain the difference between idiosyncrasy and drug allergy. **(LO 1.5)**
14. Write a short paragraph describing the terms *receptor site, binding, drug action, agonist, antagonist,* and *competitive antagonism.* **(LO 1.3)**

Acquired Knowledge

Answer the following questions.

1. Examine *Facts and Comparisons* online. Briefly describe the information found in Sections 1 through 5. **(LO 1.7)**
2. Look up the popular decongestant pseudoephedrine in Drugs@FDA online. What is your conclusion based on the available trade names? **(LO 1.7)**
3. What is a dose-response curve and what information is given by a dose-response curve? **(LO 1.4)**
4. What is the importance of a time-plasma drug concentration curve? How often would you estimate that a drug should be administered per day if the drug is eliminated in 4 hours? In 24 hours? **(LO 1.4)**
5. It is interesting that a drug can produce a therapeutic effect and an undesired side effect in one situation, and that the same side effect may be considered a therapeutic effect in another situation. Explain this phenomenon using the drug promethazine (*Phenergan*) as an example. **(LO 1.2)**
6. Obtain a copy of *Drug Facts and Comparisons* (F&C) from your school library, online, Micromedex, or UpToDate/Lexicomp. It is divided into many sections. Examine some sections and briefly explain how the following may be useful in your field. **(LO 1.7)**
   a. Table of Contents
   b. Chapters; broken down by sections on drug classifications
   c. Index

Applying Knowledge on the Job

Use your critical-thinking skills to answer the following questions.

1. Obtain a copy of the *Facts & Comparisons* from your school, nursing unit, or clinic and use it to do some sleuthing. Find the drugs that solve the following "medical mysteries." **(LO 1.7)**
   a. Dan is currently taking the drugs *Mephyton, Biaxin,* and *Entex LA* for his chronic celiac disease and acute sinusitis. He was just prescribed *Coumadin* for thrombosis, and it had no therapeutic effect. Dan's doctor suspects it's a case of drug antagonism. Which drug is Dan taking that is antagonistic with *Coumadin?*
   b. Mary's grandfather just came home from the doctor with a prescription for *Vaseretic* and he has already forgotten why he is supposed to take it. Explain what this drug is, its indications, and the most common adverse effects.
   c. Bill's young wife was just prescribed *Vibra-Tabs* for a respiratory infection. Bill asks you what this drug is and is it safe for his wife to take, since she may be pregnant. Is it safe?

2. Assume that your employer has asked you to help screen patients for potential prescription drug problems. Look up the following frequently prescribed prescription drugs in the *Facts & Comparisons* and provide the information requested. **(LO 1.7)**
   a. *Indocin:* What would tip you off that a patient was showing adverse effects to the drug?
   b. *Bicillin:* Describe symptoms of a patient who is allergic to this drug.
   c. *Depakote:* For whom is this drug contraindicated?

Use the *Facts & Comparisons* to answer the following questions.

3. a. A patient calls you and states that he has found a single loose tablet on the carpet. He needs you to identify it for him. He describes it as a small blue tablet with a heart cut out of the middle. There is writing on the tablet, but it is too small to read. What is this medication? **(LO 1.7)**
   b. A patient calls with a minor problem. While traveling, she got her medications mixed together. She needs to take her *Cordarone* tablet but isn't sure which one it is. Could you please describe it to her? **(LO 1.7)**

4. a. A physician wants to know what glucose-elevating products are available and whether they require a prescription. Look under the hormone section and find these products. List the available products, strengths, forms, and status. **(LO 1.7)**
   b. A physician wants to know the available forms and strength of *Imitrex.* Using the index, look up the medication and list the available forms, strengths, and package sizes. **(LO 1.7)**

5. Sarah Roberts has liver damage due to a past history of alcohol abuse. She is also taking carbamazepine 400 mg TID. Can she safely take acetaminophen for her chronic headaches? **(LO 1.7)**

Multiple Choice

Use your critical-thinking skills to answer the following questions. Select the correct answer.

1. The study of drug absorption, distribution, metabolism, and excretion is known as **(LO 1.1)**
   A. pharmacotherapeutics
   B. pharmacodynamics
   C. pharmacokinetics
   D. pharmacy
   E. posology

2. The medical situation when a particular drug should not be administered is referred to as **(LO 1.2)**
   A. side effect
   B. adverse effect
   C. drug allergy
   D. contraindication
   E. antagonism

3. An unusual or unexpected drug reaction by an individual is known as **(LO 1.5)**
   A. toxic effect
   B. antagonism
   C. idiosyncrasy
   D. side effect
   E. drug allergy

4. The proprietary drug name supplied by a pharmaceutical company is also referred to as the **(LO 1.6)**
   A. generic name
   B. over-the-counter name
   C. trade name
   D. chemical name
   E. none of these

5. The time from drug administration to the first observable drug effect is known as the **(LO 1.4)**
   A. duration of action
   B. onset of action
   C. ceiling effect
   D. maximal response
   E. ceiling effect

6. A drug that has the potential for abuse and is regulated by the Drug Enforcement Agency is classified as a **(LO 1.7)**
   A. poison
   B. OTC drug
   C. prescription drug
   D. controlled substance
   E. nonproprietary drug

7. Select the term that relates to the amount of drug administered to produce a therapeutic effect. **(LO 1.1)**
   A. posology
   B. toxicology
   C. pharmacodynamics
   D. pharmacotherapeutics
   E. pharmacy

8. A medication that does not require a physician's service to obtain is referred to as **(LO 1.6)**
   A. trade
   B. nonproprietary
   C. nonprescription
   D. brand
   E. generic

Chapter Review Continued

9. Which of the following could be categorized as an adverse reaction? **(LO 1.5)**
   A. idiosyncrasy
   B. drug allergy
   C. teratogenicity
   D. carcinogenicity
   E. all of these

10. The time a drug continues to produce its effect is its **(LO 1.4)**
   A. ED50
   B. maximal response
   C. ceiling effect
   D. onset of action
   E. duration of action

Chapter 2

Pharmacokinetics and Factors of Individual Variation

FatCamera/Getty Images

KEY TERMS

bioavailability: percentage of the drug dosage that is absorbed.

drug absorption: entrance of a drug into the bloodstream from its site of administration.

drug addiction: condition of drug abuse and drug dependence that is characterized by compulsive drug behavior.

drug dependence: condition of reliance on the use of a particular drug, characterized as physical and/or psychological dependence.

drug distribution: passage of a drug from the blood to the tissues and organs of the body.

drug excretion: elimination of the drug from the body.

drug metabolism: the enzymatic biotransformation of a drug into metabolites.

drug microsomal metabolizing system (DMMS): group of enzymes located primarily in the liver that function to metabolize (biotransformation) drugs.

drug tolerance: decreased drug effect occurring after repeated drug administration.

enzyme induction: increase in the amount of drug-metabolizing enzymes after repeated administration of certain drugs.

enzyme inhibition: inhibition of drug-metabolizing enzymes by certain drugs.

first-pass metabolism: drug metabolism that occurs in the intestines and liver during oral absorption of drugs into the systemic circulation.

half-life: time required for the body to reduce the amount of drug in the plasma by one-half.

individual variation: difference in the effects of drugs and drug dosages from one person to another.

intramuscular (IM) injection: route of drug administration; drug is injected into gluteal or deltoid muscles.

intravenous (IV) injection: route of drug administration; drug is injected directly into a vein.

loading dose: initial drug dose administered to rapidly achieve therapeutic drug concentrations.

maintenance dose: dose administered to maintain drug levels in blood in the therapeutic range.

oral administration: route of drug administration by way of the mouth through swallowing.

parenteral administration: route of drug administration that does not involve the gastrointestinal (GI) tract.

pharmacokinetics: describes the processes of drug absorption, drug distribution, drug metabolism, and drug excretion.

Learning Outcomes

After studying this chapter, you should be able to:

LO 2.1 list different forms of drug products and the routes by which they are administered.

LO 2.2 understand the pharmacokinetic factors that determine the absorption, distribution, metabolism, and excretion of drugs.

LO 2.3 identify how half-life, blood drug level, and bioavailability relate to drug response.

LO 2.4 list several factors of individual variation that can alter drug response.

LO 2.5 understand the drug factors that relate to pediatric drug administration.

LO 2.6 discuss the different types of drug interactions.

LO 2.7 explain the basic terminology of chronic drug administration and drug dependence.

Introduction

The familiar saying "No two people are exactly alike" applies well to the effects produced by drugs. An identical drug and dose may produce an intense response in one individual and no observable effect in another. The major reasons for this are differences in **pharmacokinetics** and various factors of **individual variation** that exist among the patient population. Pharmacokinetics is a study of the factors that determine **drug absorption**, **distribution**, **metabolism**, and **excretion**.

Individual variation is caused by a number of physical and psychological factors, including differences in age, sex, weight, genetic variation, emotional state, patient expectations (placebo effect), and the presence of other disease conditions (pathology) or other drugs. The remainder of this chapter will describe what happens to a drug between its administration and its elimination from the body. The interplay among the various biologic factors determines the actual drug response.

LO 2.1

DRUG FORMS AND ROUTES OF ADMINISTRATION

Drug Forms

Drugs are prepared in various forms for administration. The physical and chemical properties of a drug usually determine which form will be most effective. In addition to the drug, most drug products contain other ingredients that facilitate the administration and absorption of the drug. Drug preparations should always be taken exactly as prescribed. Some of the more common drug forms and preparations follow.

Aqueous Preparations

Syrups are commonly used aqueous preparations. A syrup is a solution of water and sugar to which a drug is added. Addition of flavoring agents eliminates the bitter taste of many drugs.

Alcoholic Preparations

Elixirs, spirits, tinctures, and fluid extracts are drugs dissolved in various concentrations of alcohol, usually in the range of 5 to 20 percent.

Solid and Semisolid Preparations

The solid type of preparation is most common. There are a number of different types of solid preparations available that have different purposes: For example, vaginal and rectal suppositories.

Powders

Powders are drugs or drug extracts that are dried and ground into fine particles.

Tablets

Tablets are drug powders that have been compressed into a convenient form for swallowing. They usually disintegrate in the stomach more rapidly than most other solid preparations.

Troches and Lozenges

These flattened tablets are allowed to dissolve in the mouth. They are commonly used for colds and sore throats.

Capsules

Gelatin capsules are used to administer drug powders or liquids. Gelatin capsules dissolve in the stomach, thereby releasing the drug.

Delayed-Release Products

These are usually tablets or capsules that are treated with special coatings so that various portions of the drug will dissolve at different rates. Delayed-release products usually contain the equivalent of two or three single-dose units. They are designed to produce drug effects over an extended time.

Enteric-Coated Products

Some drugs are very irritating to the stomach. Also, the gastric juices of the stomach can inactivate certain drugs. In these cases, the drug tablet or capsule is coated with an acid-resistant substance that will dissolve only in the less-acidic portions of the intestines. Enteric-coated products should be taken on an empty stomach with water, either 1 hour before or 2 hours after meals.

Suppositories

These are drugs mixed with a substance (cacao butter) that will melt at body temperature. Suppositories are intended for insertion into the rectum, urethra, or vagina.

Ointments

Ointments or salves are soft, oily substances (petrolatum or lanolin) containing a drug that is applied to the skin or, in the case of ophthalmic ointments, to the eye.

Transdermal Products

Transdermal products are administered through a bandage or patch system. The drug is released from the bandage or patch and is then absorbed through the skin into the systemic circulation. This method provides a continuous source of the drug over 24 hours or more. Nitroglycerin, estrogen, and clonidine are drugs available in this form.

Parenteral Injection

Parenteral injection involves the administration of drugs by needle and syringe. Different injection sites such as subcutaneous (SC), intramuscular (IM), intravenous (IV), and others provide different rates of drug absorption and onset of action. Parenteral injection requires the practice of sterile technique and various safety precautions.

Routes of Administration

Oral Administration

The most common routes of drug administration are oral (PO) and parenteral. **Parenteral administration** is any route that does not involve the GI tract, including inhalation, hypodermic injection, and topical application. However, when the term *parenteral* is used, most individuals think of administration by injection with a needle and syringe. The **oral administration** route is the safest and the most convenient method. Oral administration usually requires 30 to 60 minutes before significant absorption from the GI tract occurs; therefore, the onset of drug action is delayed.

Although some drugs are irritating to the stomach and may cause nausea, heartburn, and vomiting, administration of such drugs with sufficient amounts of water or with meals minimizes gastric irritation. However, food also delays drug absorption and therefore delays the onset of drug action.

Besides convenience, another advantage of oral administration is that drugs given orally can be removed (within the first few hours) by gastric lavage or induced vomiting. This procedure is often used in drug overdose (sleeping pills) or accidental poisoning.

Parenteral Administration

The most common routes of parenteral administration include intramuscular injection, intravenous injection, inhalation, and topical application. **IM injections** are usually delivered into the gluteal or deltoid muscles. Extreme caution should be observed with gluteal injections to avoid injury to the sciatic nerve. The onset of action with IM administration is relatively short, usually within several minutes. **Intravenous injection** is usually restricted to use in the hospital. IV injection offers the fastest means of drug absorption because the drug is delivered directly into the circulation; therefore, the onset of drug action is almost immediate. However, there is some degree of risk because the drug cannot be withdrawn once it has been injected. Dosage miscalculations resulting in overdose can produce serious, even fatal, consequences. Inhalation involves administration of drug through the nose or mouth and into the lungs during respiratory inspiration. This route is especially useful for the local administration of drugs into the respiratory tract. Topical application of creams and ointments is used for local effects in the skin and in certain conditions for systemic effects, as with nitroglycerin ointment for the treatment of angina pectoris.

Several other routes of administration are used in specific situations. The most commonly used routes are listed in Table 2.1 with examples of their indications for use. Other routes will be presented in the appropriate chapters.

Table 2.1

Routes of Drug Administration

Route	Approximate onset of action	Indications	Examples
Oral (PO)	30 to 60 minutes	Whenever possible, the safest and most convenient route	Most medications—aspirin, sedatives, hypnotics, antibiotics
Sublingual	Several minutes	When rapid effects are needed	Nitroglycerin in angina pectoris
Buccal	Several minutes	Convenient dosage form for certain drugs	Androgenic drugs
Rectal	15 to 30 minutes	When patient cannot take oral medications and parenteral is not indicated, also for local effects	Analgesics, laxatives
Transdermal	30 to 60 minutes	Convenient dosage form that provides continuous absorption and systemic effects over many hours	Nitroglycerin, estrogen
Subcutaneous (SC)	Several minutes	For drugs that are inactivated by the GI tract	Insulin
Intramuscular (IM)	Several minutes	For drugs that have poor oral absorption, when high blood levels are required, and when rapid effects are desired	Narcotic analgesics, antibiotics
Intravenous (IV)	Within 1 minute	In emergency situations, where immediate effects are required, also when medications are administered by infusion	IV fluids (dextrose), nutrient supplementation, antibiotics
Intraarterial	Within 1 minute	For local effects within an internal organ	Cancer drugs
Intrathecal	Several minutes	For local effects within the spinal cord	Spinal anesthesia with lidocaine
Inhalation	Within 1 minute	For local effects within the respiratory tract	Antiasthmatic medications such as epinephrine
Topical	Within 1 hour	For local effects on the skin, eye, or ear	Creams and ointments
Vaginal	15 to 30 minutes	For local effects	Creams, foams, and suppositories

LO 2.2

PHARMACOKINETIC PROCESSES

Drug Absorption

Drug absorption refers to the entrance of a drug into the bloodstream. For absorption to occur, the drug must be dissolved in body fluids. With the exception of IV or intraarterial administration, drugs must pass through membranes of the GI lining and blood vessels before they gain access to the blood. Cell membranes are composed of lipids and proteins, which form a semipermeable barrier.

Cells have special transport mechanisms that allow various substances (including drugs) to pass through the cell membrane. These mechanisms include filtration, passive transport, and active transport. Most drugs pass through membranes by passive transport. An important principle in passive transport is that the concentration of drug on each side of the membrane differs. In passive transport, drug molecules diffuse from an area

of high concentration to an area of low concentration (law of diffusion).

Note to the Health-Care Professional

It is very important for nurses and other health personnel to always follow the physician's orders and the established guidelines for the administration of drugs. One practical approach to drug administration is referred to as "the five rights." This approach advocates that the person dispensing the drug make a mental checklist that emphasizes giving the *right patient* the *right drug* in the *right dose* by the *right route* at the *right time*.

In addition, different disciplines have added more rights such as having the *proper documentation* and the *right attitude* on the part of the person administering the drug. This aspect is important for generating a positive attitude in the patient toward therapy and contributes to a positive placebo response on the part of patients.

For example, following oral administration, there is a large amount of drug in the GI tract and no drug in the blood. Consequently, the drug molecules have a natural tendency to diffuse from the GI tract into the blood. The speed or rate of drug absorption also depends on the chemical properties of the drug and other factors such as the presence of food or other drugs. The properties of the drug that most determine absorption are lipid (fat) solubility of the drug and the degree of drug ionization.

Lipid Solubility

Cell membranes are composed of a significant amount of lipid material. In general, the more lipid soluble a drug is, the faster it will pass through a lipid substance like the cell membrane. With the exception of general anesthetics (highly lipid soluble), most drugs are primarily water soluble and only partially lipid soluble. Many water-soluble drugs are weak acids or bases that can form charged particles or ions (ionization) when dissolved in body fluids. The absorption of water-soluble drugs is mainly influenced by the degree of drug ionization.

Drug Ionization

Most drugs exist in two forms: ionized and un-ionized. Like electrolytes (Na^+ and Cl^-), ionized drugs are charged molecules because their atomic structure has lost or gained electrons. The molecules then become either positively or negatively charged. In general, ionized drug molecules do not readily cross cell membranes. The un-ionized (uncharged) form of the drug is required for absorption to occur.

The first generalization is that acid drugs (aspirin) are mostly un-ionized when they are in an acidic fluid (gastric juice). Consequently, drug absorption is favored. Conversely, acid drugs are mostly ionized when they are in an alkaline fluid; therefore, absorption is not favored and occurs at a slower rate and to a lesser extent.

The second generalization is that basic drugs (streptomycin, morphine) are mostly un-ionized when they are in an alkaline fluid (lower GI tract after rectal administration). Conversely, these drugs are mostly ionized when they are dissolved in an acidic fluid like the upper GI tract. This is the reason why morphine is usually administered parenterally. In the stomach (pH 1 to 3) and upper intestinal tract (pH 5 to 6), basic drugs like morphine are absorbed more slowly and to a lesser extent than acidic drugs because they are primarily in an ionized form.

The acidic and basic nature of drugs may be useful in treating drug toxicity (overdose). Drugs are generally excreted by the kidneys in an ionized form. To increase drug excretion, the pH of the urine can be altered. For example, to increase the renal excretion of an acid drug (aspirin), the urine is alkalinized ($pH > 7$). In an alkaline urine, acidic drugs are mostly ionized and more rapidly excreted. In the same manner basic drugs are more rapidly excreted by acidifying the urine ($pH < 7$).

Drug Formulation

Drugs must be in solution before being absorbed. Tablets and capsules require time for the dissolution to occur. For this reason, liquid medications are generally absorbed faster than the solid forms. Drug particles can be formulated into different sizes, such as crystals, micronized particles, or ultramicronized particles. The smaller the size of the drug particle, the faster the rate of dissolution and absorption.

Drug Distribution

After a drug gains access to the blood, it is distributed to the various tissues and organs of the body. Several factors determine how much drug reaches any one organ or area of the body. The main factors are plasma protein binding, blood flow, and the presence of specific tissue barriers.

Plasma Protein Binding

Several different proteins (albumin and globulins) are in the plasma and form a circulating protein pool. These plasma proteins help regulate osmotic pressure (oncotic pressure) in the blood and transport many hormones and vitamins. In addition, many drugs are attracted to the plasma proteins, especially albumin. The result is that some drug molecules are bound to plasma proteins while some drug molecules are unbound (free in the circulation). Only the unbound or free drug molecules can exert a pharmacologic effect. The ratio of the bound to unbound drug molecules varies with the drug used. Some drugs are highly bound (99 percent), while other drugs are not bound to any significant degree.

Occasionally, there is competition between drugs or other plasma substances for the same plasma protein binding site. In this situation, one drug may displace another. The result is that the concentration of free drug of one of the drugs increases, and this concentration can lead to increased pharmacologic and adverse effects similar to overdosage.

Blood Flow

The various organs of the body receive different amounts of blood. Organs such as the liver, kidneys, and brain have the largest blood supply. Consequently, these organs are usually exposed to the largest amount of drug. Some tissues, such as adipose tissue, receive a relatively poor blood supply and, as a result, do not accumulate large amounts of drug. However, highly lipid-soluble drugs can enter adipose tissue easily, where they can accumulate and remain for an extended period of time.

Blood–Brain Barrier

In the case of the brain, an additional consideration is the blood–brain barrier. This barrier is an additional lipid barrier that protects the brain by restricting the passage of electrolytes and other water-soluble substances. Since the brain is composed of a large amount of lipid (nerve membranes and myelin), lipid-soluble drugs pass readily into the brain. As a general rule, then, a drug must have a certain degree of lipid solubility if it is to penetrate this barrier and gain access to the brain.

Drug Metabolism

Whenever a drug or other foreign substance is taken into the body, the body attempts to eliminate it. This usually involves excretion by one of the normal excretory routes (renal, intestinal, or respiratory). Some drugs can be excreted in the same chemical form in which they were administered. Other drugs, however, must be chemically altered before they can be excreted by the kidneys. Drug metabolism, also referred to as biotransformation, is the chemical alteration of drugs and foreign compounds in the body.

The liver is the main organ involved in drug metabolism. Within the cells of the liver are a group of enzymes that specifically function to metabolize foreign (drug) substances. These enzymes are referred to as the **drug microsomal metabolizing system (DMMS)**. The DMMS utilizes cytochrome P450 enzymes that are important in oxidation and reduction reactions that convert drugs into their metabolites. The main function of this system is to take lipid-soluble drugs and chemically alter them so that they become water-soluble compounds. Water-soluble compounds can be excreted by the kidneys. Lipid-soluble compounds are repeatedly reabsorbed into the blood. Although most drugs are inactivated by metabolism, a few are initially converted into pharmacologically active metabolites.

An interesting phenomenon occurs with some drugs, especially the barbiturates and other sedative-hypnotic drugs. When these drugs are taken repeatedly, they stimulate the drug microsomal metabolizing system. By stimulating this system, the drugs actually increase the amount of enzymes (cytochrome P450s) in the system; this process is referred to as **enzyme induction**. With an increase in the amount of enzymes, there is a faster rate of drug metabolism. Consequently, the duration of drug action is decreased for all drugs metabolized by the microsomal enzymes. In addition, other drugs can inhibit the drug microsomal metabolizing enzymes to cause **enzyme inhibition**. This action slows the metabolism of all other drugs metabolized by these enzymes. This will increase the duration and intensity of the drugs inhibited. Enzyme induction and enzyme inhibition are common causes of adverse drug interactions.

After oral administration, all drugs are absorbed into the portal circulation, which transports the drugs to the liver before they are distributed throughout the body. Some drugs are metabolized significantly as they pass through the liver this first time. This effect is referred to as **first-pass metabolism**. It can significantly reduce bioavailability and the amount of active drug that reaches the general circulation.

Drug Excretion

The common pathways of drug excretion are renal (urine), GI (feces), and respiratory (exhaled gases). Although the liver is the most important organ for drug metabolism, the kidneys are the most important organs for drug excretion.

Renal Excretion

After the blood is filtered through the glomerulus of the kidneys, most of the filtered substances are eventually reabsorbed into the blood. The exceptions to this are the urinary waste products and anything else that is in a nonabsorbable form. For drug excretion to occur, the drug or drug metabolite must be water soluble and preferably in an ionized form. As mentioned, acid drugs are mostly ionized in alkaline urine and basic drugs are mostly ionized in an acid urine. In the case of barbiturate or aspirin overdose (acid drugs), alkalinization of the urine with sodium bicarbonate will hasten elimination of either drug in the urine.

GI Excretion

After oral administration, a certain portion of drug (unabsorbed) passes through the GI tract and is excreted in the feces. The amount varies with the particular drug used.

In addition, there is another pathway involving the intestinal tract, the enterohepatic pathway. Certain drugs (fat-soluble drugs) can enter the intestines by way of the biliary tract. After the drug is released into the intestines (in the bile), it may be absorbed from the intestines back into the blood again. This is referred to as the enterohepatic cycle. The duration of action of a few drugs is greatly prolonged because of this repeated cycling of the drug (liver → bile → intestines → blood → liver).

Respiratory Excretion

The respiratory system does not usually play a significant role in drug excretion. However, some drugs are metabolized to products that can be exchanged from the blood into the respiratory tract. General anesthetic gases are not totally metabolized. These drugs are excreted primarily by the lungs.

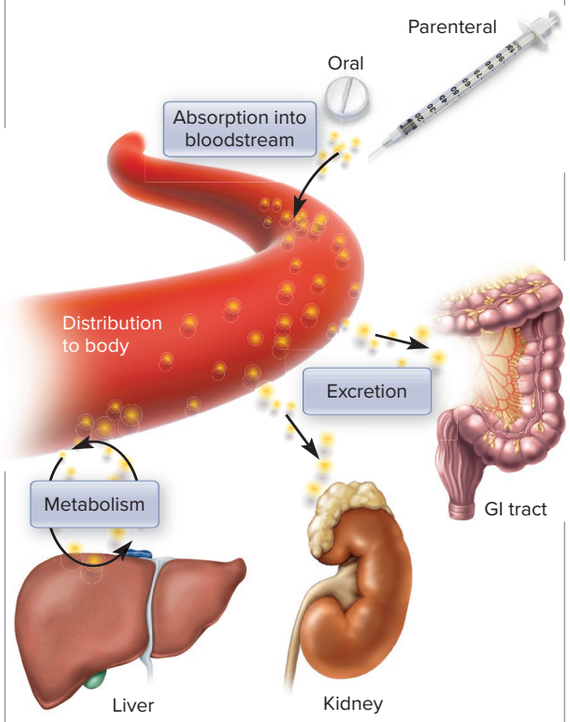
Miscellaneous

Some drugs and drug metabolites also can be detected in sweat, saliva, and milk (lactation). Infants can be exposed to significant amounts of certain drugs after nursing (see the Drug Exposure During Infant Nursing section).

In summary, following drug administration, the processes of drug absorption and distribution predominate as the drug is absorbed into the bloodstream and distributed to the various tissues. Later, drug metabolism and excretion predominate as the drug is eliminated from the body. However, once some drug reaches the bloodstream, it is distributed to the liver and kidneys, which then begin metabolism and excretion. Consequently, all of the pharmacokinetic processes occur simultaneously to varying degrees depending on the time since administration. Figure 2.1 illustrates the interrelationship of the pharmacokinetic processes.

Figure 2.1

Movement of Drug in the Body



Following absorption the drug is distributed to all the tissues of the body. The liver metabolizes the drug so that the metabolites can be excreted by the kidneys and GI tract.

LO 2.3

CLINICAL FACTORS THAT DETERMINE THE INTENSITY OF DRUG RESPONSE

Half-Life

The **half-life** of a drug is the time required for the blood or plasma concentration of the drug to fall to half of its original level. For example, after two half-lives only 25 percent of the drug that was absorbed remains in the blood. Half-life is important in determining the frequency of drug administration. To maintain a continuous drug effect, the drug must be given at intervals that keep the plasma concentration above the minimal effective concentration. The major factors that determine half-life are the rates of drug metabolism and excretion. The half-life of any drug is relatively constant if the individual has normal rates of drug metabolism and excretion. It can be prolonged when liver or kidney disease is present. In these situations, the dose or the frequency of administration can be reduced.

Blood Drug Levels

The intensity of drug effect is mainly determined by the concentration of drug in the blood or plasma. The drug effect and the amount of drug in the plasma are determined by an interplay among all of the pharmacokinetic processes (absorption, distribution, metabolism, and excretion) and the pharmacodynamics (pharmacologic effects) of the drug (Figure 2.2). As a drug is absorbed and distributed, the liver and kidneys begin the processes of metabolism and excretion. As long as the drug concentration in the plasma is within the therapeutic range, the drug concentration at the site of action will be sufficient to produce the pharmacodynamic or pharmacologic effect.

Drug monitoring, the periodic measurement of blood drug levels, is performed to ensure that the level of drug in the blood is within the therapeutic range. Drug levels below the therapeutic range will not produce the desired drug effect, while levels above the therapeutic range cause increased side effects and toxicity. This concept is illustrated in Figure 2.3.

There are some drugs that require several dosages or several days or weeks to reach the desired drug effect. In some clinical situations, it may be necessary to reach therapeutic drug levels as rapidly as possible. In these cases, a loading dose may be administered. A **loading dose** is usually an initial higher dose of drug, often administered IV, to rapidly attain the therapeutic drug level and drug effects. Loading doses are usually followed by **maintenance doses** that are smaller and calculated to maintain the drug level within the therapeutic range.

Bioavailability

Bioavailability is the percentage of the dose of a drug that is actually absorbed into the bloodstream. Differences in drug formulation, route of administration, and factors that affect GI absorption can influence bioavailability. A particular drug may be manufactured by many different drug companies and sold under different trade names. In these situations, the amount of drug may be the same in each product, but the product may be different because of particle size, binders, fillers, and tablet coating. These differences may alter bioavailability. There have been examples of this in the past. Now, however, the Food and

Figure 2.2 Illustration of the Relationship Between the Pharmacokinetic and Pharmacodynamic Processes That Determine the Pharmacologic and Clinical Drug Response

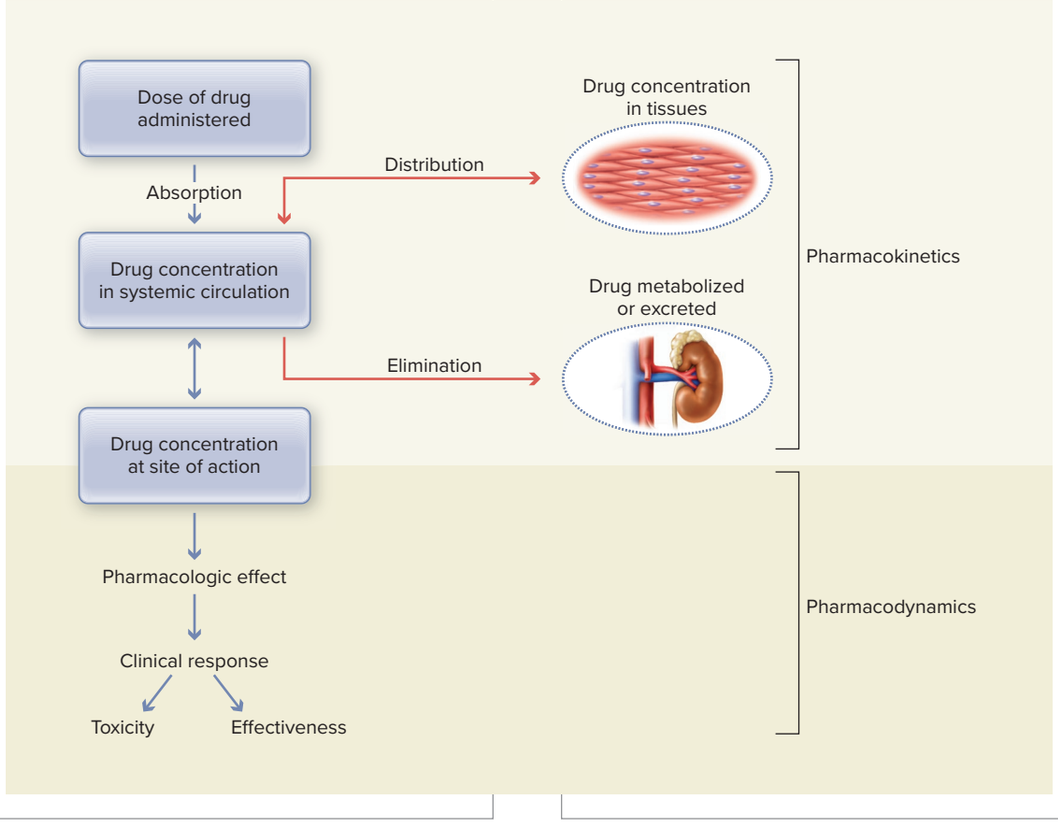
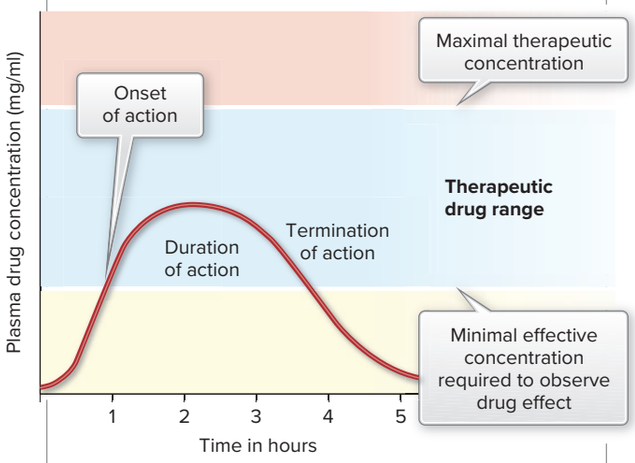


Figure 2.3

Illustration of the Therapeutic Drug Range



Drug Administration (FDA) regulates and requires bioavailability testing.

LO 2.4

FACTORS OF INDIVIDUAL VARIATION

Many factors affect individual variation. These factors include age, weight, sex, genetic variation, emotional state, placebo effect, the presence of disease, and patient compliance.

Age

The effects of drugs in different age groups is of particular importance. Infants, children, and the elderly are generally more sensitive to the actions of drugs than are younger adults. Drug considerations during pregnancy on fetal development, during the infant nursing period, and in infants and children are discussed in the section Pharmacokinetic Considerations for Pediatrics. Drug considerations for the elderly are presented in Chapter 3.

Weight

Most adult dosages are calculated for the average adult weight, 150 pounds between the ages of 16 and 65. Obviously, all adults are not 150 pounds. In small individuals (100 pounds), the dose may have to be reduced. In larger individuals (200 to 300 pounds), the dose may have to be increased. However, this approach does not always hold true, since many other factors are involved.

Sex and Percent Body Fat

Females possess a higher percentage of body fat and a lower percentage of body water than do males of equal weight. Consequently, females may experience a greater drug effect than do males because the drug is dissolved in a smaller volume of body fluid. Lipid-soluble drugs are more widely distributed and may produce longer durations of action in females than in males. This same concept also applies to the differences in body fat composition between members of the same sex.

Genetic Variation

Individuals tend to inherit the proteins and enzyme patterns of their parents. There is significant genetic variation in some of the drug-metabolizing enzymes, so individual differences can occur. If the difference affects the rate of drug metabolism, there may be a difference in the effects produced by the drug. An enzyme may be missing, in which case drug metabolism is extremely slow. A slowed metabolic rate may result in increased and prolonged drug effects that can lead to serious consequences. Examples of genetic variation will be discussed in specific chapters.

Emotional State

Differences in drug effects can be caused by the emotional state of the individual. For example, an individual who is excited or extremely anxious may require a larger dose of hypnotic or tranquilizer than an individual who is not emotionally stimulated but who still has difficulty sleeping.

Placebo Effect

Patients come to physicians and hospitals with varying expectations. It has been observed that if patients have a positive attitude and think that the drug or treatment will help, chances are the patients claim an improvement whether there actually is one or not.

In some studies, patients have been unknowingly given sugar pills or placebos instead of an actual drug. A large percentage of these patients claim an improved condition even though they received no real drug. Likewise, patients with hostile or negative attitudes, who feel that nothing will help their condition, usually say that they feel no difference or even worse after a specific treatment or medication. The influence of one's mind on the course of treatment is referred to as the placebo effect. This phenomenon can be used by the medical and nursing staff to enhance the positive attitude of patients. Thus, the patients stand a better chance of responding successfully to therapy.

Presence of Disease

The presence of other diseases that are debilitating or that decrease the function of some vital organ usually makes an individual more susceptible to the effects and adverse reactions of drug therapy. As mentioned, the liver and kidneys are especially important, since these two organs are exposed to the highest drug levels. For this reason, liver and kidney functions are often adversely affected by drugs. Patients with hepatic or renal disease suffer a greater incidence of adverse drug effects because they are unable to eliminate the drug and its metabolites effectively. Consequently, plasma drug levels are much higher in these patients due to accumulation of the drug in the plasma.

Patient Compliance

Drug compliance refers to taking a drug exactly as prescribed. If dosages are forgotten or skipped, the drug effects will be reduced or absent. This is referred to as noncompliance. Noncompliance is often a problem in geriatric patients who may have memory difficulties and who are easily confused by complicated dosing schedules, especially when several different drugs are involved. Particular care and sufficient patient instructions and training must be given to ensure that all patients understand dosing instructions.

LO 2.5

PHARMACOKINETIC CONSIDERATIONS FOR PEDIATRICS

Fetal Period During Pregnancy

Before birth the developing fetus will be exposed to most drugs taken during pregnancy. The placenta is not a drug barrier, and drug absorption and distribution to the fetus follow the same principles as with other maternal organs (passive diffusion based on lipid solubility and ionization). Although there are relatively few drugs that have been proven to be teratogenic (cause birth defects), it is recommended that drug exposure during pregnancy should be avoided if possible. This is especially true during the first trimester when organogenesis, the formation of body organs, is occurring. Drugs that are teratogens may cause spontaneous abortion, growth retardation, birth defects, or carcinogenesis (development of cancer). The FDA has established guidelines, or pregnancy categories (Table 2.2), that classify drugs based on fetal risk. Table 2.3 lists some drugs that have been associated with teratogenicity in humans. Consult *Facts & Comparisons* for an expanded list of drugs assigned to the FDA Pregnancy Categories.

Table 2.2

Description of FDA Pregnancy Categories

Pregnancy category	Description
A	Drug studies in pregnant women have not yet demonstrated risk to the fetus
B	Drug studies have not been performed in pregnant women; animal studies have not demonstrated fetal risk
C	Drug studies have not been performed in pregnant women or in animals, or animal studies have revealed some teratogenic potential but the risk to the fetus is unknown
D	Drug studies have revealed adverse risk to the fetus. The benefit-to-risk ratio of the drug must be established before use during pregnancy
X	Drug studies have revealed teratogenic effects in women and/or animals. Fetal risk clearly outweighs benefit. Drug is contraindicated in pregnancy
NR	Drug has not yet been rated by FDA

Table 2.3

Examples of Drugs with Demonstrated Teratogenic Risk in Humans

Drug	Teratogenic effect
Androgens (male hormone)	Masculinization of female fetus
Carbamazepine	Craniofacial and fingernail deformities
Diethylstilbestrol	Vaginal tumors and genital malformations in offspring
Estrogen (female hormone)	Feminization of male fetus
Lithium	Cardiac defects
Phenytoin	Craniofacial and limb deformities, growth retardation
Retinoic acid	Craniofacial, cardiac, and *CNS defects
Thalidomide	Phocomelia (limb deformities)
Warfarin	Facial, cartilage, and CNS defects

*Abbreviations: *CNS, central nervous system*

Drug Exposure During Infant Nursing

Drugs administered to nursing mothers appear in breast milk to varying degrees. Unfortunately there is a lack of controlled studies and reliable information in this area. The major concern is that the drug concentration in the milk will be high enough to produce undesired or harmful effects in the infant. Generally, the recommendation is to avoid unnecessary drug administration. Usually the infant experiences the same pharmacologic effects as in the mother. For example, laxatives may cause infant diarrhea, while sedatives and hypnotics will cause drowsiness and lethargy. Other drugs such as anticancer agents or drugs with increased toxicities are contraindicated unless the benefit to the mother clearly outweighs the risk to the infant. Table 2.4 lists some of the drugs that appear in breast milk.

Pediatric Considerations

There are a number of pharmacokinetic and pharmacodynamic differences between pediatric and adult patients. Neonates (0 to 1 month), infants (1 to 12 months), and children of increasing age are not simply "small adults." There are a number of factors that must be considered that generally require reduction in dosage beyond the obvious difference in body weight. These differences tend to decrease with advancing age, especially after the first year of life.

Drug Administration and Absorption

Neonates and infants have a small skeletal muscle mass. In addition, limited physical activity results in a lower blood flow to muscle. Therefore, absorption after IM injections is slower and more variable. There is also increased risk of muscle and nerve damage with IM injections. In serious situations the IV route is more reliable and generally preferred. The skin of neonates and infants is thinner and topically applied drugs are more rapidly and completely absorbed into the systemic circulation. With regard to oral administration, the gastric pH of premature babies and neonates is less acidic. This could result in decreased bioavailability and lower blood levels of orally administered drugs that are acidic in nature.

Drug Distribution

Pediatric patients possess a higher percentage of body water and a lower percentage of body fat. These differences decrease the distribution of lipid-soluble drugs to body tissues and organs. This tends to cause higher drug levels in blood. Water-soluble drug distribution is increased (greater peripheral drug distribution), which

Table 2.4

Examples of Drugs That Cross into Breast Milk Following Maternal Use

Drug class	Examples
Antibiotics	Ampicillin, erythromycin, penicillin, streptomycin, sulfa drugs, tetracyclines
Antiepileptic agents	Phenytoin, primidone
Antithyroid agents	Thiouracil
CNS stimulants	Nicotine
Laxatives	Cascara
Narcotic analgesics	Codeine, heroin, methadone, morphine
Sedative-hypnotic agents	Barbiturates, chloral hydrate
Tranquilizers (antipsychotic agents)	Chlorpromazine, lithium

Diane McDonald/Getty Images

tends to lower drug levels in blood. These effects are all in comparison to the adult effects. While pediatric patients have higher percentages of water, they are more easily dehydrated by vomiting and diarrhea. The resulting reduction of body fluids will increase drug concentrations and drug effects.

Plasma protein levels are also lower, especially in neonates. This results in lower plasma protein binding of drugs and, therefore, greater amounts of unbound or "free" drug. Since only the unbound drug exerts an effect, there will be a greater intensity of drug effect.

Drug Metabolism and Excretion

There is a reduced capacity for drug metabolism and drug excretion during the first several years of life. Consequently, drug elimination occurs more slowly and the duration of drug action is prolonged. The decreases in drug metabolism and excretion are most evident in neonates and infants. After the first year, drug metabolism and excretion gradually become proportional to those of the adult.

Dosage Adjustment

Dosage calculations in pediatrics are based mainly on age, body surface area, and body weight. The rules and formulas used for these calculations are presented in Chapter 4.

LO 2.6

DRUG INTERACTIONS

Drug interaction refers to the effects that occur when the actions of one drug are affected by another drug. There are many different types of drug interactions. Some drugs interfere with each other during GI absorption and therefore should not be administered at the same time. Other drugs may interfere with plasma protein binding, drug metabolism, or drug excretion. Throughout this book, the common drug interactions will be given. Table 2.5 explains the general terms that are associated with drug interactions.

LO 2.7

TERMINOLOGY ASSOCIATED WITH CHRONIC DRUG USE AND ABUSE

The chronic use of certain drugs results in a number of physiologic and pharmacologic changes in drug response. Drug tolerance and drug dependence are two important phenomena involved in chronic drug use.

Tolerance

Drug tolerance is defined as a decreased drug effect that occurs after repeated administration. To attain the

Table 2.5

Terminology of Common Drug Interactions

Term	Explanation
Incompatibility	Usually refers to physical alterations of drugs that occur before administration when different drugs are mixed in the same syringe or other container
Additive effects	When the combined effect of two drugs, each producing the same biologic response by the same mechanism of action, is equal to the sum of their individual effects
Summation	When the combined effect of two drugs, each producing the same biologic response but by a different mechanism of action, is equal to the sum of their individual effects
Synergism	When the combined effect of two drugs is greater than the sum of their individual effects
Antagonism	When the combined effect of two drugs is less than the sum of their individual effects

previous drug effect, the dosage must be increased. This is a common occurrence in individuals who abuse drugs such as cocaine, barbiturates, morphine, and heroin. There is also the phenomenon of cross-tolerance, which is the tolerance that exists between drugs of the same class. Tolerance is caused by changes or adaptations that occur in response to repeated drug exposure. The main types of tolerance are referred to as metabolic tolerance and pharmacodynamic tolerance. Metabolic tolerance is caused by enzyme induction—the drug increases the drug-metabolizing enzymes (DMMS) and the dose must be increased to attain the same previous effect. Pharmacodynamic tolerance is caused by the ability of some drugs to decrease the number of drug receptors. This usually takes several weeks or months and is referred to as down-regulation. With the reduction in drug receptors there is a reduction in the intensity of drug effect.

Drug Dependence

Drug dependence is a condition wherein reliance on the administration of a particular drug becomes extremely important to the well-being of an individual. Drug dependence is usually characterized as psychological and/or physical. When the drug is used repeatedly for nonmedical purposes, the term *drug abuse* is applied. Any activity that is repeated and that provides pleasure involves a psychological component of behavior. The smoking of tobacco, for example, is an activity associated with psychological dependence. Deprivation of smoking causes some unpleasant feelings, but does not result in serious medical consequences. All drugs that are abused have varying degrees of psychological dependence associated with them. Many abused drugs also produce physical dependence when taken for prolonged periods of time and usually at increasing dosages. Deprivation of these drugs leads to a physical withdrawal syndrome that is very unpleasant, characterized by measurable changes in many bodily functions, and that may cause serious medical consequences. The withdrawal reactions from alcohol, barbiturates, and opiate drugs are examples of this type of reaction. When drug dependence is particularly severe and compulsive drug behavior dominates all other activities, the term **drug addiction** is used. Information concerning tolerance and dependence of specific drug classes can be found in Chapters 12, 13, 15, and 19.