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THIRD EDITION

CASE FILES™ Pharmacology

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Mc Graw Hill Education | Medical

New York Chicago San Francisco Athens London Madrid Mexico City
Milan New Delhi Singapore Sydney Toronto

ISBN: 978-0-07-179024-6

MHID: 0-07-179024-1

e-book conversion by Cenveo® Publisher Services

Version 1.0

The material in this eBook also appears in the print version of this title: ISBN: 978-0-07-179023-9, MHID: 0-07-179023-3.

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DEDICATION

To Dr. Larry C. Gilstrap III, whose encouragement is largely responsible for my writing this series of books. He has been a personal inspiration, mentor, and role model of an outstanding physician, teacher, and leader; and to Dr. Edward Yeomans, who has been a dear friend and gleaming light of brilliance in obstetrics.

—ECT

To the medical and graduate students of the UT Health Medical School in Houston who continually challenge and make both teaching and research far more interesting; and to my son William and innumerable colleagues for their patience and encouragement during the writing and editing of the manuscript.

—DSL

To my patients, who humble me with their trust and respect; to my residents, students, and colleagues who challenge, teach, and inspire me; and of course to my family who support and encourage my passion.

—ASP

To my students, who continue to provide inspiration.

—SAT

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ACKNOWLEDGMENTS

The inspiration for this basic science series occurred at an educational retreat led by Dr. L. Maximilian Buja, who at the time was the dean of the medical school. It has been such a joy to work together with Dr. David Loose, who is an accomplished scientist and teacher. It has been rewarding to collaborate with Dr. Anush Pillai, a scholar and an excellent teacher. It has been a pleasure to work with our new author Dr. Shelley Tischkau, who is both a content expert and an excellent educator. I would like to thank McGraw-Hill for believing in the concept of teaching by clinical cases. I owe a great debt to Catherine Johnson, who has been a fantastically encouraging and enthusiastic editor.

At the University of Texas Medical School at Houston, we would like to recognize the bright and enthusiastic medical students who have inspired us to find better ways to teach. At The Methodist Hospital, I appreciate the support from Drs. Mark Boom, Judy Paukert, and Alan Kaplan. At St. Joseph Medical Center, I would like to recognize some of the finest administrators I have encountered: Pat Mathews, John Bertini, MD, and Thomas V. Taylor, MD. I appreciate Linda Bergstrom's excellent advice and assistance. Without the help from my colleagues and friends, Drs. Konrad Harms, Priti Schachel, Gizelle Brooks-Carter, and John C. McBride, this book could not have been written. Most importantly, I am humbled by the love, affection, and encouragement from my lovely wife, Terri, and our four children, Andy, Michael, Allison, and Christina.

Eugene C. Toy, MD

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Often, the medical student will cringe at the "drudgery" of the basic science courses and see little connection between a field such as pharmacology and clinical problems. Clinicians, however, often wish they knew more about the basic sciences, because it is through the science that we can begin to understand the complexities of the human body and thus have rational methods of diagnosis and treatment.

Mastering the knowledge in a discipline such as pharmacology is a formidable task. It is even more difficult to retain this information and to recall it when the clinical setting is encountered. To accomplish this synthesis, pharmacology is optimally taught in the context of medical situations, and this is reinforced later during the clinical rotations. The gulf between the basic sciences and the patient arena is wide. Perhaps one way to bridge this gulf is with carefully constructed clinical cases that ask basic science-oriented questions. In an attempt to achieve this goal, we have designed a collection of patient cases to teach pharmacology-related points. More importantly, the explanations for these cases emphasize the underlying mechanisms and relate the clinical setting to the basic science data. The principles are explored rather than overemphasizing rote memorization.

This book is organized for versatility: to allow the student "in a rush" to go quickly through the scenarios and check the corresponding answers and to provide more detailed information for the student who wants thought-provoking explanations. The answers are arranged from simple to complex: a summary of the pertinent points, the bare answers, a clinical correlation, an approach to the pharmacology topic, a comprehension test at the end for reinforcement or emphasis, and a list of references for further reading. The clinical cases are arranged by system to better reflect the organization within the basic science. Finally, to encourage thinking about mechanisms and relationships, we used open-ended questions in the clinical cases. Nevertheless, several multiple-choice questions are included at the end of each scenario to reinforce concepts or introduce related topics.

HOW TO GET THE MOST OUT OF THIS BOOK

Each case is designed to introduce a clinically related issue and includes open-ended questions usually asking a basic science question, but at times, to break up the monotony, there will be a clinical question. The answers are organized into four different parts:

Part I

1. **Summary**
2. **A straightforward answer** is given for each open-ended question.
3. **Clinical Correlation—**A discussion of the relevant points relating the basic science to the clinical manifestations, and perhaps introducing the student to issues such as diagnosis and treatment.

Part II

An **approach to the basic science concept** consisting of three parts:

1. **Objectives—**A listing of the two to four main knowledge objectives that are critical for understanding the underlying pharmacology to answer the question and relate to the clinical situation.
2. **Definitions of basic terminology.**
3. **Discussion of the specific class of agents.**

Part III

Comprehension Questions—Each case includes several multiple-choice questions that reinforce the material or introduces new and related concepts. Questions about the material not found in the text are explained in the answers.

Part IV

Pharmacology Pearls—A listing of several important points, many clinically relevant, reiterated as a summation of the text and to allow for easy review, such as before an examination.

SECTION I

Applying the Basic Sciences to Clinical Medicine

Part 1. Approach to Learning Pharmacology

Pharmacology is best learned by a systematic approach, understanding the physiology of the body, recognizing that **every medication has desirable and undesirable effects**, and being aware that the biochemical and pharmacologic properties of a drug affects its characteristics such as duration of action, volume of distribution, passage through the blood-brain barrier, mechanism of elimination, and route of administration. Rather than memorizing the characteristics of a medication, the student should strive to learn the underlying rationale such as, "Second-generation antihistamine agents are less lipid soluble than first-generation antihistamines and therefore do not cross the blood-brain barrier as readily; thus, second-generation antihistamines are not as sedating. Because they both bind the histamine H_1 receptor, the efficacy is the same."

KEY TERMS

Pharmacology: The study of substances that interact with living systems through biochemical processes.

Drug: A substance used in the prevention, diagnosis, or treatment of disease.

Toxicology: A branch of pharmacology that studies the undesirable effects of chemicals on living organisms.

Food and Drug Administration (FDA): The federal agency responsible for the safety and efficacy of all drugs in the United States, as well as food and cosmetics.

Adverse effect: Also known as side effect; all unintended actions of a drug that result from the lack of specificity of drug action. All drugs are capable of producing adverse effects.

Pharmacodynamics: The actions of a drug on a living organism, including mechanisms of action and receptor interaction.

Pharmacokinetics: The actions of the living organism on the drug, including absorption, distribution, and elimination.

Volume of distribution (V_d): The size of the "compartment" into which a drug is distributed following absorption and is determined by the equation:

$$V_d = \text{Dose (mg) drug administered/Initial plasma concentration (mg/L)}$$

Potency of drug: Relative amount of drug needed to produce a given response, determined largely by the amount of drug that reaches the site of action and by the affinity of the drug for the receptor.

Efficacy: Drug effect as the maximum response it is able to produce and is determined by the number of drug-receptor complexes and the ability of the receptor to be activated once bound. **EC-50** refers to the drug concentration that produces 50 percent of the maximal response, whereas **ED-50** refers to the drug dose that is pharmacologically effective in 50 percent of the population.

Absorption: The movement of a drug from the administration site into the blood stream usually requiring the crossing of one or more biologic membranes. Important parameters include lipid solubility, ionization, size of the molecule, and presence of a transport mechanism.

Elimination: Process by which a drug is removed from the body, generally by either metabolism or excretion. Elimination follows various kinetic models. For example, **first-order kinetics** describes most circumstances, and means that the rate of drug elimination depends on the concentration of the drug in the plasma as described by the equation:

$$\textit{Rate of elimination from body} = \textit{Constant} \times \textit{Drug concentration}$$

Zero-order kinetics: It is less common and means that the rate of elimination is constant and does not depend on the plasma drug concentration. This may be a consequence of a circumstance such as saturation of liver enzymes or saturation of the kidney transport mechanisms.

Bioavailability: The percentage of an ingested drug that is actually absorbed into the bloodstream.

Route of administration: Drug may be delivered **intravenously** (IV or iv) for delivery directly into the bloodstream, **intramuscularly** (IM), and **subcutaneously** (SC). The medication may be depot and slow release, **inhalant** for rapid absorption and delivery to the bronchi and lungs, **sublingual** to bypass the first-pass effect, **intrathecal** for agents that penetrate the blood-brain barrier poorly, **rectal** to avoid hepatic first-pass effect and for nausea, and **topical** administration when local effect is desired such as dermatologic or ophthalmic agents.

Part 2. Approach to Disease

Physicians usually tackle clinical situations by taking a history (asking questions), performing a physical examination, obtaining selective laboratory and imaging tests, and then formulating a diagnosis. The synthesis of the history, physical examination, and imaging or laboratory tests is called the **clinical database**. After reaching a diagnosis, a treatment plan is usually initiated, and the patient is followed for a clinical response. Rational understanding of disease and plans for treatment are best acquired by learning about the normal human processes on a basic science level; likewise, being aware of how disease alters the normal physiologic processes is also best understood on a basic science level. Pharmacology and therapeutics require also the ability to tailor the correct medication to the patient's situation and awareness of the medication's adverse effect profile. Sometimes, the patient has an adverse reaction to a medication as the chief complaint, and the physician must be able to identify the medication as the culprit. An understanding of the underlying basic science allows for more rational analysis and medication choices.

Part 3. Approach to Reading

There are seven key questions that help to stimulate the application of basic science information to the clinical setting. These are:

1. **Which of the available medications is most likely to achieve the desired therapeutic effect and/or is responsible for the described symptoms or signs?**

2. **What is the likely mechanism for the clinical effect(s) and adverse effect(s) of the medication?**
3. **What is the basic pharmacologic profile (e.g., absorption, elimination) for medications in a certain class, and what are the differences among the agents within the class?**
4. **Given basic pharmacologic definitions such as therapeutic index (TI) or certain safety factor (TD_1/ED_{99}), or median lethal dose (LD_{50}), how do medications compare in their safety profile?**
5. **Given a particular clinical situation with described unique patient characteristics, which medication is most appropriate?**
6. **What is the best treatment for the toxic effect of a medication?**
7. **What are the drug-drug interactions to be cautious about regarding a particular medication?**

1. **Which of the following medications is most likely to be responsible for the described symptoms or signs?**
   The student must be aware of the various effects, both desirable and undesirable, produced by particular medications. Knowledge of desirable therapeutic effects is essential in selecting the appropriate drug for the particular clinical application; likewise, an awareness of its adverse effects is necessary, because patients may come into the physician's office with a complaint caused by a drug effect unaware that their symptoms are because of a prescribed medication. It is only by being aware of the common and dangerous effects that the clinician can arrive at the correct diagnosis. The student is encouraged not to merely memorize the comparative adverse effect profiles of the drugs, but rather to understand the underlying mechanisms.
2. **What is the likely mechanism for the clinical effect(s) and adverse effect(s) of the medication?**
   As noted above, the student should strive to learn the underlying physiologic, biochemical, or cellular explanation for the described drug effect. This understanding allows for the rational choice of an alternative agent or the reasonable choice of an agent to alleviate the symptoms or explanatory advice to the patient regarding behavioral changes to diminish any adverse affects. For example, if a 60-year-old woman who takes medications for osteoporosis complains of severe "heartburn," one may be suspicious, knowing that the bisphosphonate medication alendronate can cause esophagitis. Instruction to the patient to take the medication while sitting upright and remaining upright for at least 30 minutes would be the proper course of action, because gravity will assist in keeping the alendronate in the stomach rather than allowing regurgitation into the distal esophagus.

3. **What is the basic pharmacologic profile (absorption, elimination, volume of distribution) for medications in a certain class, and what are differences among the agents within the class?**
   Understanding the pharmacologic profile of medications allows for rational therapeutics. However, instead of memorizing the separate profiles for every medication, grouping the drugs together into classes allows for more efficient learning and better comprehension. An excellent starting point for the student of pharmacology would be to study how a **prototype drug** within a drug class organized by structure or mechanism of action may be used to treat a condition (such as hypertension). Then within each category of agents, the student should try to identify important subclasses or drug differences. For example, hypertensive agents can be categorized as diuretic agents, β-adrenergic-blocking agents, calcium-channel-blocking agents, and renin-angiotensin system inhibitors. Within the subclassification of renin-angiotensin system inhibitors, the angiotensin-converting enzyme inhibitors can cause the side effect of a dry cough caused by the increase in bradykinin brought about by the enzyme blockade; instead, the angiotensin-1 receptor blockers do not affect the bradykinin levels and so do not cause the cough as often.

4. **Given basic pharmacologic definitions such as therapeutic index (TI) or certain safety factor (TD_1/ED_{99}), or median lethal dose (LD_{50}), how do medications compare in their safety profile?**

   Therapeutic index (TI): Defined as the TD_{50}/ED_{50} (the ratio of the dose that produces a toxic effect in half the population to the dose that produces the desired effect in half the population).

   Certain safety factor (TD_1/ED_{99}): Defined as the ratio of the dose that produces the toxic effect in 1 percent of the population to the dose that produces the desired effect in 99 percent of the population; also known as **standard safety measure.**

   Median lethal dose (LD_{50}): Defined as the median lethal dose, the dose that will kill half the population.

   Based on these definitions, a desirable medication would have a high therapeutic index (toxic dose is many times that of the efficacious dose), high certain safety factor, and high median lethal dose (much higher than therapeutic dose). Likewise, medications such as digoxin that have a low therapeutic index require careful monitoring of levels and vigilance for side effects.

5. **Given a particular clinical situation with described unique patient characteristics, which medication is most appropriate?**
   The student must weigh various advantages and disadvantages, as well as different patient attributes. Some of those may include compliance with medications, allergies to medications, liver or renal insufficiency, age, coexisting medical disorders, and other medications. The student must be able to sift through the medication profile and identify the most dangerous adverse effects. For example, if a patient is already taking a monoamine-oxidase-inhibiting agent for depression, then adding a serotonin reuptake inhibitor would be potentially fatal, because serotonin syndrome may ensue (hyperthermia, muscle rigidity, death).

6. **What is the best treatment for the toxic effect of a medication?**
If complications of drug therapy are present, the student should know the proper treatment. This is best learned by understanding the drug mechanism of action. For example, a patient who has taken excessive opioids may develop respiratory depression, caused by either a heroin overdose or pain medication, which may be fatal. The treatment of an opioid overdose includes the ABCs (airway, breathing, circulation) and the administration of naloxone, which is a competitive antagonist of opioids.

7. **What are the drug-drug interactions to be concerned with regarding a particular medication?**
Patients are often prescribed multiple medications, from either the same practitioner or different clinicians. Patients may not be aware of the drug-drug interactions; thus, the clinician must compile, as a component of good clinical practice, a current list of all medications (prescribed, over-the-counter, and herbal) taken by the patient. Thus, the student should be aware of the most common and dangerous interactions; once again, understanding the underlying mechanism allows for lifelong learning rather than short-term rote memorization of facts that are easily forgotten. For example, magnesium sulfate to stop preterm labor should not be used if the patient is taking a calcium-channel-blocking agent such as nifedipine. Magnesium sulfate acts as a competitive inhibitor of calcium, and by decreasing its intracellular availability it slows down smooth muscle contraction such as in the uterus. Calcium-channel blockers potentiate the inhibition of calcium influx and can lead to toxic effects, such as respiratory depression.

COMPREHENSION QUESTIONS

I.1 Bioavailability of an agent is maximal when the drug has which of the following qualities?

A. Highly lipid soluble
B. More than 100 Daltons in molecular weight
C. Highly bound to plasma proteins
D. Highly ionized

I.2 An agent is noted to have a very low calculated volume of distribution (V_d). Which of the following is the best explanation?

A. The agent is eliminated by the kidneys, and the patient has renal insufficiency.
B. The agent is extensively bound to plasma proteins.
C. The agent is extensively sequestered in tissue.
D. The agent is eliminated by zero-order kinetics.

I.3 Which of the following describes the first-pass effect?

A. Inactivation of a drug as a result of the gastric acids.

B. Absorption of a drug through the duodenum.

C. Drug given orally is metabolized by the liver before entering the circulation.

D. Drug given IV accumulates quickly in the central nervous system (CNS).

I.4 A laboratory experiment is being conducted in which a mammal is injected with a noncompetitive antagonist to the histamine receptor. Which of the following best describes this agent?

A. The drug binds to the histamine receptor and partially activates it.

B. The drug binds to the histamine receptor but does not activate it.

C. The drug binds to the receptor, but not where histamine binds, and prevents the receptor from being activated.

D. The drug irreversibly binds to the histamine receptor and renders it ineffective.

I.5 A 25-year-old medical student is given a prescription for asthma, which the physician states has a very high therapeutic index. Which of the statements best characterizes the drug as it relates to the therapeutic index?

A. The drug's serum levels will likely need to be carefully monitored.

B. The drug is likely to cross the blood-brain barrier.

C. The drug is likely to have extensive drug-drug interactions.

D. The drug is unlikely to have any serious adverse effects.

I.6 A drug M is injected IV into a laboratory subject. It is noted to have high serum protein binding. Which of the following is most likely to be increased as a result?

A. Drug interaction

B. Distribution of the drug to tissue sites

C. Renal excretion

D. Liver metabolism

I.7 A bolus of drug K is given IV. The drug is noted to follow first-order kinetics. Which of the following describes the elimination of drug K?

A. The rate of elimination of drug K is constant.

B. The rate of elimination of drug K is proportional to the patient's renal function.

C. The rate of elimination of drug K is proportional to its concentration in the patient's plasma.

D. The rate of elimination of drug K is dependent on a nonlinear relationship to the plasma protein concentration.

ANSWERS

I.1 **A.** Transport across biologic membranes and thus bioavailability is maximal with high lipid solubility.

I.2 **B.** The volume of distribution is calculated by administering a known dose of drug (mg) IV and then measuring an initial plasma concentration (mg/L). The ratio of the mass of drug given (mg) divided by the initial plasma concentration (mg/L) gives the V_d. A very low V_d may indicate extensive protein binding (drug is sequestered in the bloodstream), whereas a high V_d may indicate extensive tissue binding (drug is sequestered in the tissue).

I.3 **C.** The first-pass effect refers to the process in which following oral administration a drug is extensively metabolized as it initially passes through the liver, before it enters the general circulation. Liver enzymes may metabolize the agent to such an extent that the drug cannot be administered orally.

I.4 **C.** A noncompetitive antagonist binds to the receptor at a site other than the agonist-binding site and renders it less effective by preventing agonist binding or preventing activation.

I.5 **D.** An agent with a high therapeutic index means the toxic dose is very much higher than the therapeutic dose, and it is less likely to produce toxic effects at therapeutic levels.

I.6 **A.** High protein binding means less drug to the tissue, the kidney, and the liver. Drug interaction may occur if the agent binds to the same protein site as other drugs, thus displacing drugs and increasing serum levels.

I.7 **C.** First-order kinetics means the rate of elimination of a drug is proportional to the plasma concentration.

PHARMACOLOGY PEARLS

- Understanding the pharmacologic mechanisms of medications allows for rational choices for therapy, fewer medication errors, and rapid recognition and reversal of toxic effects.
- The therapeutic index, certain safety factor (TD_1/ED_{99}), and median lethal dose are various methods of describing the potential toxicity of medications.
- There are seven key questions to stimulate the application of basic science information to the clinical arena.

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SECTION II

Clinical Cases

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CASE 1

A 12-year-old female with an unremarkable past medical history (PMH) presents with fever, sore throat, and a tender cervical lymphadenopathy. She is diagnosed with streptococcal Group A pharyngitis and is treated with IM penicillin. Within a few minutes of the injection, the patient is dyspneic, tachycardic, and hypotensive, and is noted to have wheezing on examination. She also complains of dysphagia. IM epinephrine is administered immediately for her anaphylactic reaction.

- What effect will epinephrine have on this patient's vascular system?
- Which adrenoceptor primarily mediates the vascular response?
- What effect will epinephrine have on her respiratory system?
- Which adrenoceptor primarily mediates the respiratory system response?

ANSWERS TO CASE 1:
Autonomic Sympathetic Nervous System

Summary: A 12-year-old girl with "strep throat" is given an injection of penicillin and develops an acute anaphylactic reaction.

- **Effect of epinephrine on vascular system:** Vasoconstriction.
- **Adrenoceptor which primarily mediates the vascular response:** Alpha-1 (α_1).
- **Effect of epinephrine on the pulmonary system:** Bronchial muscle relaxation.
- **Adrenoceptor which primarily mediates the pulmonary response:** Beta-2 (β_2).

CLINICAL CORRELATION

Anaphylaxis is an acute, immune-mediated response to an allergen characterized by bronchospasm, wheezing, tachycardia, and hypotension. Epinephrine is the drug of choice used to treat this condition because it counteracts the pathophysiologic processes underlying anaphylaxis through the activation of alpha (α)- and beta (β)-adrenoceptors. As with all emergencies, the ABCs (airway, breathing, circulation) should be addressed first. Occasionally, anaphylaxis causes laryngeal edema to the extent that the airway is compromised, and intubation (placement of a tube in the trachea) is impossible. In these circumstances, an emergency airway, such as a surgical cricothyroidotomy (creating an opening from the skin through the cricoid cartilage), is required. **The appropriate dose:** In children, 0.01 mg per kilogram body weight (1 mg/mL preparation) or a maximum dose of 0.5 mg can be given intramuscularly and can be repeated every 5 to 25 minutes as needed. In adults, 0.3 to 0.5 mg (1 mg/mL preparation).

APPROACH TO:
The Autonomic Sympathetic Nervous System

OBJECTIVES

1. List the neurotransmitters of the autonomic sympathetic nervous system and describe their anatomical localization.
2. List the receptors and receptor subtypes of the autonomic sympathetic nervous system.
3. Predict the responses to activation and inhibition of autonomic sympathetic nervous system receptors.

DEFINITIONS

Autonomic nervous system: Subdivision of the peripheral nervous system that is largely controlled unconsciously, shown in Figure 1–1.

Sympathetic nervous system: A division of the autonomic nervous system (the other is the parasympathetic nervous system). Preganglionic fibers originate in the CNS and are carried on the **thoracic and lumbar spinal nerves** to synapse on ganglia close to the spinal cord. Synapses also occur on the adrenal medulla, which is considered a modified ganglion. Postganglionic fibers innervate a wide variety of effector organs and tissues, including arteriole and bronchial smooth muscles.

Agonist: A molecule (drug) that binds to and activates a receptor, resulting in a response.

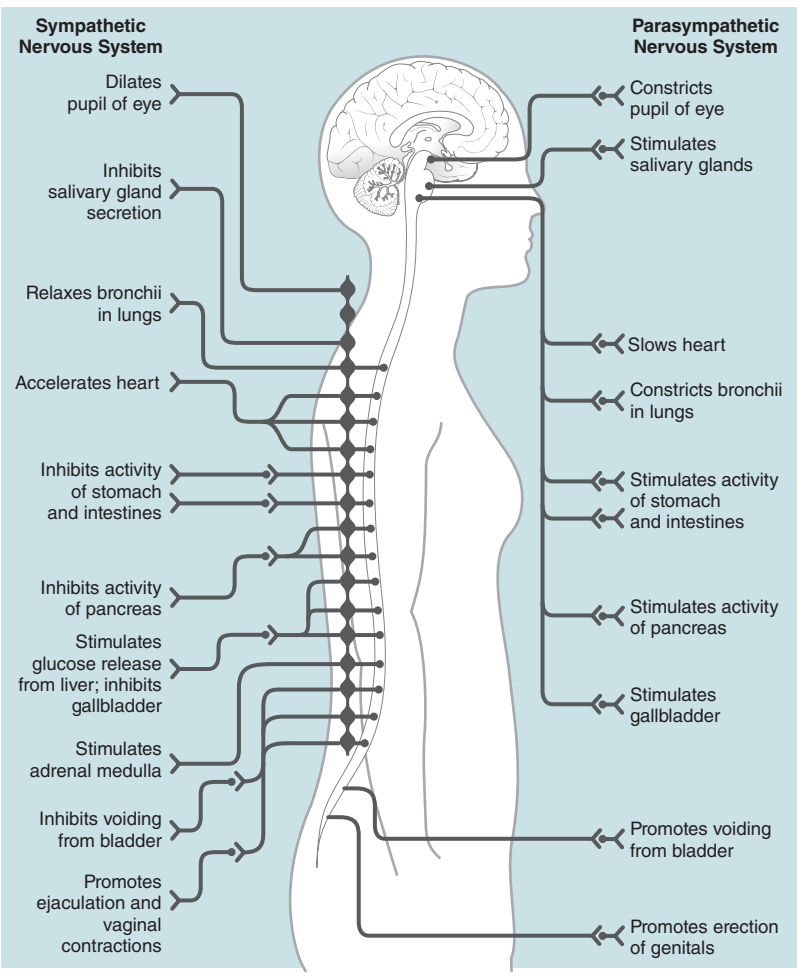

Figure 1–1. Schematic of autonomic nervous system.

Antagonist: A molecule (drug) that binds to receptors with little or no effect of its own, but that can block the action of an agonist that binds to the same receptors.

Mydriasis: Dilatation of the eye pupil.

DISCUSSION

Class

Endogenous **catecholamines** are the typical neurotransmitters released from postganglionic nerve terminals. The neurotransmitter **norepinephrine** is released from the efferent nerves of the **sympathetic autonomic nervous system** at postganglionic sympathetic (also known as "adrenergic") nerve endings. **Epinephrine and some norepinephrine** are released from the **adrenal medulla.**

Catecholamine agonists interact at postsynaptic **adrenoceptors** (named after the adrenergic nerves that innervate them) that are classified as either alpha (α) or beta (β).

There are two **subtypes of the α-adrenoceptor, α_1 and α_2.** Activation of the α_1-adrenoceptors by adrenergic agonists results in **contraction of most vascular smooth muscle (α_1)** causing increased peripheral resistance and blood pressure, **contraction of the pupillary dilator muscle** resulting in **mydriasis, relaxation of gastrointestinal smooth muscle and contraction of gastrointestinal sphincters** (α_1, indirectly through inhibition of acetylcholine [Ach] release), and **ejaculation.** Activation of presynaptic adrenoceptor autoreceptors (α_2) by catecholamines results in (feedback) inhibition of the release of norepinephrine and other neurotransmitters from their respective nerve endings.

There are **three subtypes of the β-adrenoceptor, β_1, β_2, and β_3.** Activation of β-adrenoceptors by adrenergic agonists results in increased rate and **force of contraction of the heart (β_1), smooth muscle relaxation of bronchi causing bronchodilation (β_2),** and activation of **fat cell lipolysis** (β_3).

Because the catecholamines epinephrine and norepinephrine have important physiologic roles, drugs that block their actions, that is, adrenoceptor antagonists, can have important, and clinically useful, pharmacologic effects. **α-Adrenoceptor nonselective antagonists** (eg, phentolamine) are used to treat the hypertension of **pheochromocytoma** (a tumor that secretes catecholamines) and **male erectile dysfunction,** whereas the more selective **α_1-adrenoceptor antagonists** (eg, prazosin, terazosin, doxazosin) are used to treat **hypertension and benign prostatic hyperplasia** (Table 1–1).

Structure

Epinephrine and norepinephrine are catecholamines, **synthesized from tyrosine,** that possess a catechol nucleus with an ethylamine side chain (epinephrine is the methylated side chain derivative of norepinephrine). The **rate-limiting enzyme** in this process is **tyrosine hydroxylase.**

Mechanism of Action

Epinephrine binding to α_1-adrenoceptors activates a G-protein (Gq-type GTP-binding protein [Gq]) to stimulate phospholipase C, resulting in the formation

Table 1–1 • SELECTED EFFECTS OF ADRENOCEPTOR ACTIVATION

Organ	Effects (Adrenoceptor Subtype)
Bronchial smooth muscle	Dilates (β_2)
Heart rate and contractile force	Increases (β_1)
Eye (pupil size)	Dilates (α_1)*
Blood vessels	Constrict (α_1)†,‡
Gastrointestinal tract (tone, motility, secretions)	Decrease (α_1, β_2)
Pancreas (insulin release)	Decrease (α_2)

*__Dilation (mydriasis)__ results from α_1-adrenoceptor stimulation of the radial muscle.
†Skeletal muscle blood vessels have β_2-adrenoceptors that, when activated, result in **vessel constriction.**
‡Coronary arteries also have β-adrenoceptors that, when activated, result in **vessel dilation,** which is the dominant effect.

of inositol 1,4,5-trisphosphate (IP_3) to promote release of Ca^{2+} from intracellular stores. Epinephrine interaction with α_2-adrenoceptors activates a Gi-type GTP-binding protein (Gi) to inhibit adenylyl cyclase activity and decreases intracellular cyclic adenosine monophosphate (cAMP). Epinephrine perhaps also increases β_1-adrenoceptor-mediated influx of Ca^{2+} across membrane channels.

In addition to the increased formation of the **second messenger, IP_3,** epinephrine also increases the phospholipase-mediated formation of another second messenger diacylglycerol (DAG) that activates protein kinase C to influence a number of other signaling pathways. Epinephrine also activates **β_1- and β_2-adrenoceptors to increase a G-protein-mediated stimulation of adenylyl cyclase activity,** thereby **increasing intracellular cAMP levels** and the activity of cAMP-dependent protein kinases.

Administration

Epinephrine is generally administered **parenterally** (IM) for treatment of anaphylactic shock. For this and other conditions, it is also available as IV, SC, ophthalmic, nasal, and aerosol preparations. Norepinephrine is only available for parenteral, generally IV, administration.

Pharmacokinetics

Epinephrine released from the adrenal gland is metabolized primarily by catechol-O-methyltransferase (COMT) and monoamine oxidase (MAO). The action of norepinephrine released from nerve endings is terminated primarily by reuptake into nerve terminals (uptake 1) and other cells (uptake 2).

COMPREHENSION QUESTIONS

1.1 A 33-year-old patient with septic shock is noted to have persistent hypotension despite IV dopamine infusion. The patient is treated with an IV infusion of epinephrine. With which adrenoceptor does epinephrine act to constrict vascular smooth muscle?

A. α_1-Adrenoceptors
B. α_2-Adrenoceptors
C. β_1-Adrenoceptors
D. β_2-Adrenoceptors

1.2 A 16-year-old male is having an acute asthmatic attack. Epinephrine is given via SC route. Through which of the following adrenoceptors does epinephrine act to dilate bronchial smooth muscle?

A. α_1-Adrenoceptors
B. α_2-Adrenoceptors
C. β_1-Adrenoceptors
D. β_2-Adrenoceptors

1.3 Which of the following best describes the cellular action of epinephrine?

A. Activation of adenylyl cyclase
B. Decreased activity of cAMP-dependent protein kinases
C. Increased intracellular stores of Ca^{2+}
D. Inhibition of the activity of phospholipase

1.4 Epinephrine-mediated β_1-adrenoceptor activation results in which of the following?

A. Constriction of bronchial smooth muscle
B. Decreased gastrointestinal motility
C. Dilation of the pupils
D. Increased heart rate

ANSWERS

1.1 **A.** α_1-Adrenoceptors mediate vasoconstriction in many vascular beds. In skeletal muscle, epinephrine can act on β_2-adrenoceptors to cause vasodilation.

1.2 **D.** Epinephrine acts on β_2-adrenoceptors to cause smooth muscle relaxation of bronchi resulting in bronchodilation. Because of adverse cardiovascular effects of epinephrine (β_1), more selective β_2-adrenoceptor agonists are now used (eg, albuterol).

1.3 **A.** Epinephrine activates α_1-adrenoceptors to cause a release of intracellular stored Ca^{2+} and β_1- and β_2-adrenoceptors to activate adenylyl cyclase.

1.4 **D.** Epinephrine activation of β_1-adrenoceptors results in an increase in heart rate. Activation of α_1-adrenoceptors results in dilation of the pupil. Activation of β_2-adrenoceptors causes dilation of bronchial smooth muscle and decreased gastrointestinal (GI) motility.

PHARMACOLOGY PEARLS

- Physiologically, epinephrine acts as a hormone on distant cells after its release from the adrenal medulla.
- Sympathetic postganglionic neurons that innervate sweat glands and renal vascular smooth muscle release ACh and dopamine, respectively. All other sympathetic postganglionic neurons release norepinephrine.
- Epinephrine/norepinephrine mediates the physiological "fight or flight" response. When trying to escape a lion, eyes dilate to improve your near vision, all sphincters constrict, heart rate increases to optimize pumping of blood, peripheral vascular resistance improves to prevent syncope, bronchodilation occurs to improve oxygenation, and increased vascular flow to skeletal muscle helps maneuver out of the situation.
- Exogenously administered epinephrine increases blood pressure through its action on β_1-adrenoceptors in the heart, resulting in increased heart rate and force of contraction and through its action on β_1-adrenoceptors in many vascular beds that results in vasoconstriction.
- In skeletal muscle, epinephrine injection can result in vasodilation (β_2) that in some cases may lead to a decreased total peripheral resistance and a decrease in diastolic pressure.
- Norepinephrine has little, if any, effect on β_2-adrenoceptors (norepinephrine and epinephrine have similar effects on α- and β_1-adrenoceptors), thus increasing both systolic and diastolic blood pressure.

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CASE 2

A 25-year-old woman presents to the general medicine clinic complaining of vision problems. She has difficulty keeping her eyes open and complains of "seeing double." Her symptoms fluctuate throughout the day. Her ptosis is more common in the left eye, but will switch over to the right eye. Her symptoms are generally better in the morning and worsen as the day progresses. Her ptosis seems to get better after she rests her eyes. She exercises regularly, but has noticed that over the past 2 months she has struggled to complete her evening run due to fatigue in her hips. You suspect myasthenia gravis and perform an edrophonium (Tensilon) test. The test is positive and therefore the patient is started on mestinon.

- How does the edrophonium test aid in the diagnosis of myasthenia gravis?
- What are the mechanisms of action of edrophonium and mestinon?

ANSWERS TO CASE 2:
Muscarinic Cholinomimetic Agents

Summary: A 25-year-old woman is diagnosed with myasthenia gravis and treated with mestinon.

- **Edrophonium test and diagnosis:** An intramuscular or intravenous injection of edrophonium will alleviate ptosis by temporarily increasing the availability of acetylcholine at the synapse, allowing contraction of the levator palpebrae superiorus muscle. This test is very specific for diagnosing myasthenia gravis.
- **Mechanisms of action of edrophonium and mestinon:** acetylcholinesterase (AChE) inhibitors.

CLINICAL CORRELATION

Myasthenia gravis is an autoimmune disorder in which the patient produces autoantibodies against the acetylcholine (ACh) receptor. These autoantibodies most frequently target the nicotinic receptors found in the motor end plate of skeletal muscle. Over time, the number of ACh receptors in the synapse is significantly reduced. Thus, the disease is characterized by weakness and fatigability of skeletal muscle. More than 50 percent of patients present with ocular problems, including ptosis and diplopia. Proximal limb muscles (hip and shoulder), as well as muscles of respiration, are frequently affected. Symptoms typically fluctuate throughout the day, are worse in the evening and with exertion, and are relieved with rest. The thymus is thought to be important in the generation of autoantibodies; symptoms are often relieved after thymectomy. AChE inhibitors are mainstays of treatment for myasthenia gravis. They suppress the metabolism of ACh, thereby increasing its presence in the synapse, allowing sustained synaptic transmission, and muscle contraction.

APPROACH TO:
Muscarinic Cholinomimetic Agents

OBJECTIVES

1. List the receptors of the parasympathetic nervous system.
2. Contrast the actions and effects of direct and indirect stimulation of muscarinic cholinoreceptors.
3. List the therapeutic uses of parasympathomimetic agents.
4. List the adverse effects of parasympathomimetic agents.

DEFINITIONS

Parasympathetic nervous system: An anatomic division of the autonomic nervous system (the other is the sympathetic nervous system). Preganglionic fibers are carried on **cranial and sacral spinal nerves** to synapse on ganglia that give rise to short postganglionic fibers, many of which are in the organs they innervate.

Cholinomimetic agents: Agents that **mimic the action of ACh.** These act directly or indirectly to activate **cholinoreceptors.** Directly acting agents (pilocarpine, bethanechol, carbachol) are designed to act selectively on either muscarinic or nicotinic cholinoreceptors, whereas indirectly acting agents (such as neostigmine, physostigmine, edrophonium, demecarium), which inhibit the enzyme AChE that is responsible for the metabolism of ACh, can activate both. Pilocarpine is a directly acting cholinomimetic agent that acts chiefly at muscarinic cholinoreceptors. Additional selectivity of pilocarpine and other cholinomimetics in the treatment of glaucoma is achieved by the use of an ophthalmic (topical) preparation.

Ptosis: Drooping of the eyelids.

Diplopia: Double vision.

DISCUSSION

Class

The **efferent nerves of the parasympathetic autonomic nervous system** release the **neurotransmitter ACh** at both preganglionic and postganglionic (ie, "cholinergic") nerve endings, and also at somatic nerve endings. Nitric oxide is a cotransmitter at many of the parasympathetic postganglionic sites. The **ACh** released from nerve endings of the parasympathetic nervous system interacts at specialized cell membrane components called cholinoreceptors that are classified as either **nicotinic or muscarinic** after the alkaloids initially used to distinguish them.

Nicotinic cholinoreceptors are localized at **all postganglionic neurons** (the autonomic ganglia), including the adrenal medulla, as well as skeletal muscle endplates innervated by somatic nerves. **Muscarinic cholinoreceptors** are localized at **organs** innervated by parasympathetic postganglionic nerve endings, for example, on **cardiac atrial muscle, sinoatrial node cells, and atrioventricular node cells,** where activation can cause a **negative chronotropic effect** and delayed atrioventricular conduction. Cholinergic stimulation of **muscarinic receptors** in the **smooth muscle, exocrine glands, and vascular endothelium** can cause, respectively, **bronchoconstriction, increased acid secretion, and vasodilation** (Table 2–1).

There are **two subtypes of the nicotinic cholinoreceptors** in the periphery: $\mathbf{N_N}$, localized to **postganglionic neurons, and** $\mathbf{N_M}$, localized to **the skeletal muscle endplates.** There are five subtypes of the **muscarinic cholinoreceptors,** $\mathbf{M_1}$, $\mathbf{M_2}$, $\mathbf{M_3}$, $\mathbf{M_4}$, and $\mathbf{M_5}$; the last two are found only in the CNS. $\mathbf{M_1}$, $\mathbf{M_2}$, **and** $\mathbf{M_3}$ are localized to sympathetic postganglionic neurons (and the CNS), to the atrial muscle, sinoatrial (SA) cells, and atrioventricular (AV) node of the heart, to smooth muscle, to exocrine glands, and to the vascular endothelium that does not receive parasympathetic innervation. Directly acting cholinergic muscarinic receptor agonists are divided into two groups, **ACh** and the synthetic choline esters **(ACh, methacholine, carbachol, and bethanechol)** and the cholinomimetic alkaloids **(pilocarpine, muscarine,**

Table 2–1 • EFFECTS OF CHOLINORECEPTOR ACTIVATION

Organ	Effects
Bronchial smooth muscle	Contracts
Heart rate	Decreases
Eye smooth muscles	Contract
Pupil size	Contracts
Accommodation	
Blood vessels	Dilate*
Gastrointestinal tract (tone, motility, secretions)	Increase

*There is no parasympathetic innervation of blood vessels. However, they have cholinoreceptors that when activated result in their dilation.

and areocoline). Indirectly acting muscarinic agents act primarily by inhibiting the metabolism of ACh, through blocking the **acetylcholinesterase (AChE)** enzyme, thereby increasing the availability of naturally occurring ACh in the synapse. AChE inhibitors commonly used in the treatment of autonomic pathologies include **physiostigmine, neostigmine, pyridostigmine, and ambedonium**.

Directly and indirectly acting parasympathetic cholinomimetic agents, primarily pilocarpine and bethanechol, and neostigmine, are used most often therapeutically to treat certain diseases of the eye (acute angle-closure glaucoma), the urinary tract (urinary tract retention), the gastrointestinal tract (postoperative ileus), salivary glands (xerostomia), and the neuromuscular junction (myasthenia gravis). The **ACh** is generally not used clinically because of its numerous actions and **very rapid hydrolysis by AChE and pseudocholinesterase.**

The adverse effects of direct- and indirect-acting cholinomimetics result from cholinergic excess and may include **diarrhea, salivation, sweating, bronchial constriction, vasodilation, and bradycardia.** Nausea and vomiting are also common. Adverse effects of cholinesterase inhibitors (most often as a result of toxicity from pesticide exposure, eg, **organophosphates**) also may include **muscle weakness, convulsions, and respiratory failure.**

Structure

ACh is a choline ester that is not very lipid soluble because of its **charged quaternary ammonium group**. It **interacts with both muscarinic and nicotinic cholinoreceptors**. Choline esters similar in structure to ACh that are used therapeutically include methacholine, carbachol, and bethanechol. Unlike ACh and carbachol, **methacholine and bethanechol are highly selective for muscarinic cholinoreceptors**. Pilocarpine is a tertiary amine alkaloid.

Mechanism of Action

Muscarinic cholinoreceptors activate **inhibitory G-proteins (Gi)** to stimulate the activity of **phospholipase C,** which, through increased phospholipid metabolism, results in **production of inositol triphosphate (IP_3)** and **diacylglycerol (DAG)** that lead to the mobilization of **intracellular calcium** from the endoplasmic and

sarcoplasmic reticulum. Through activation of protein kinase C (PK-C), muscarinic cholinoreceptor activation leads to the opening of smooth muscle calcium channels causing an influx of extracellular calcium. Activation of muscarinic cholinoreceptors also increases potassium flux resulting in cell hyperpolarization, and inhibition of adenylyl cyclase activity and cAMP accumulation induced by other hormones, including the catecholamines.

The **nicotinic receptor** functions as a **cell membrane ligand-gated ion channel pore**. Upon interaction with ACh, the receptor undergoes a conformational change that results in **influx of sodium** with membrane depolarization of the nerve cell or the skeletal muscle neuromuscular endplate.

Indirectly acting parasympathetic cholinomimetic agents inhibit AChE and thereby increase ACh levels at both muscarinic and nicotinic cholinoreceptors.

Administration

Directly acting muscarinic cholinomimetic agents may be administered topically as ophthalmic preparations (pilocarpine, carbachol), orally (bethanechol, pilocarpine), or parenterally (bethanechol). Depending on the agent, an indirectly acting cholinesterase inhibitor may be administered topically, orally, or parenterally.

Pharmacokinetics

ACh is synthesized from choline and acetyl-coenzyme A (acetyl-CoA) by the enzyme choline acetyltransferase and then transported into nerve ending vesicles. Like ACh, methacholine, carbachol, and bethanechol are poorly absorbed by the oral route and have limited penetration into the CNS. **Pilocarpine is more lipid soluble and can be absorbed and can penetrate the CNS.**

After release from nerve endings, ACh is rapidly metabolized into choline and acetate, and its effects are terminated by the action of the enzymes AChE and pseudocholinesterase. Methacholine and particularly carbachol and bethanechol are resistant to the action of cholinesterases.

COMPREHENSION QUESTIONS

2.1 A 62-year-old woman is noted to have open-angle glaucoma. She inadvertently applies excessive pilocarpine to her eyes. This may result in which of the following?

A. Bronchial smooth muscle dilation
B. Decreased gastrointestinal motility
C. Dilation of blood vessels
D. Mydriasis

2.2 Muscarinic cholinergic agonists

A. Activate inhibitory G-proteins (Gi)
B. Decrease production of IP_3
C. Decrease release of intracellular calcium
D. Inhibit the activity of phospholipase C

2.3 Choline esters like carbachol are most likely to cause which of the following adverse effects?

A. Anhydrosis (dry skin)
B. Delirium
C. Salivation
D. Tachycardia (rapid heart rate)

ANSWERS

2.1 **C.** Excessive pilocarpine may initially result in dilation of blood vessels with a drop in blood pressure and a compensatory reflex stimulation of heart rate. Higher levels will directly inhibit the heart rate. In addition, pilocarpine stimulation of muscarinic cholinoreceptors can result in miosis, bronchial smooth muscle dilation, and increased GI motility.

2.2 **A.** In addition to activating inhibitory G-proteins (Gi), muscarinic cholinergic agonists stimulate the activity of phospholipase C, increase production of IP_3, and increase release of intracellular calcium.

2.3 **C.** Diarrhea, salivation, and lacrimation may be seen. The heart rate is usually slowed. Choline esters do not cross the blood-brain barrier, and therefore delirium is not an adverse effect.

PHARMACOLOGY PEARLS

- Cholinoreceptors are classified as either nicotinic or muscarinic.
- Muscarinic cholinoreceptors are localized at organs such as the heart, causing a negative chronotropic effect.
- Stimulation of muscarinic receptors in the smooth muscle, exocrine glands, and vascular endothelium cause bronchoconstriction, increased acid secretion, and vasodilation.
- Methacholine and bethanechol are highly selective for muscarinic cholinoreceptors.
- Cholinomimetic agents, including anticholinesterase inhibitors, are precluded for treatment of gastrointestinal or urinary tract disease because of mechanical obstruction, where therapy can result in increased pressure and possible perforation. They are also not indicated for patients with asthma.

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CASE 3

A 53-year-old woman comes to see you for a consultation. She is scheduled to take a Caribbean cruise in 2 weeks but is concerned about sea sickness. She has been on boats before and is very sensitive to motion sickness. A friend mentioned to her that there is a patch that is effective for this problem. She is in good health and takes no medications regularly. Her examination is normal. You prescribe a scopolamine transdermal patch for her.

- What is the mechanism of action of scopolamine?
- What are the common side effects of this medication?
- What are some relative contraindications to its use?

ANSWERS TO CASE 3:
Muscarinic Cholinoreceptor Antagonists

Summary: A 53-year-old woman with motion sickness is prescribed transdermal scopolamine before she takes a sea cruise.

- **Mechanism of action of scopolamine:** Competitive antagonist of muscarinic cholinoreceptors in the vestibular system and the CNS.
- **Common side effects:** Mydriasis, dry mouth, tachycardia, urinary retention, confusion, drowsiness.
- **Relative contraindications:** Glaucoma, urinary obstruction, heart Disease.

CLINICAL CORRELATION

Scopolamine, like other antimuscarinic agents, including the prototype atropine, is a selective competitive (surmountable) antagonist of ACh at muscarinic cholinoreceptors. Its actions can be overcome by increased concentrations of ACh or other muscarinic cholinoreceptor agonists. **Scopolamine blocks muscarinic cholinoreceptors in the vestibular system and CNS to prevent motion sickness.** It has a relatively long duration of action and can be given as a transdermal patch, making it well suited for the treatment of motion sickness. Histamine H_1-receptor antagonists, such as cyclizine, are also used to treat motion sickness.

In addition to motion sickness, muscarinic cholinoreceptor antagonists (eg, benztropine) are used therapeutically to treat **Parkinson disease**. Short-acting topical agents or ointments are used to facilitate ophthalmoscopic examination (eg, cyclopentolate, tropicamide). Ipratropium bromide, a quaternary ammonium compound that does not cross the blood-brain barrier, is used to treat asthma and has efficacy in chronic obstructive pulmonary disease (COPD). They (eg, trospium, tolterodine) are also used to treat certain bladder disorders. Because it penetrates the CNS, the tertiary amine atropine is used to counter the muscarinic cholinoreceptor effects of cholinergic excess resulting from organophosphate insecticide poisoning.

The **adverse effects of scopolamine and other muscarinic cholinoreceptor antagonists** are related to inhibition of muscarinic cholinoreceptors in organ systems of the body. **Drowsiness and sedation are caused by actions on the CNS. Mydriasis** is caused by blocking parasympathetic tone in the muscles of the cilia and iris, which could increase intraocular pressure in a person with **glaucoma.** Cholinoreceptor blockade at the sinoatrial node results in **tachycardia,** which could cause **arrhythmias,** especially in someone with underlying heart disease. The **urinary bladder is relaxed** and the **urinary sphincter constricted,** which may promote **urinary retention.** Blockade of muscarinic cholinoreceptors in the salivary glands **reduces salivation,** causing **dry mouth.** Blockade of other muscarinic cholinoreceptors in the CNS can lead to **impairment of memory, confusion, restlessness, drowsiness, or hallucinations.**

Muscarinic cholinoreceptor antagonist drugs are used cautiously in patients with **angle-closure glaucoma (contraindicated), open-angle glaucoma, urinary**

tract obstruction (eg, prostatic hypertrophy), **cardiac disease, and gastrointestinal infections,** among other conditions. Elderly patients are particularly sensitive to CNS effects.

APPROACH TO:

Muscarinic Cholinoreceptor Antagonists

OBJECTIVES

1. Describe the mechanism of action of muscarinic cholinoreceptor antagonists.
2. Describe the physiologic effects of muscarinic cholinoreceptor antagonists.
3. List important therapeutic uses of muscarinic cholinoreceptor antagonists.
4. List the adverse effects and contraindications for muscarinic cholinoreceptor antagonists.

DEFINITIONS

Chronic obstructive pulmonary disease (COPD): Progressive, inflammatory lung conditions, including both chronic bronchitis and emphysema, which result in airway obstruction that is not fully reversible. Most COPD is due to smoking.

Asthma: An inflammatory lung condition characterized by reversible airway obstruction that can be precipitated by irritants such as environmental allergens, cigarette smoke, cold air, or exercise.

Muscarinic cholinoreceptor antagonists: Drugs that block the actions of acetylcholine.

DISCUSSION

Class

Cholinoreceptor antagonists are distinguished by their specificity for muscarinic and nicotinic cholinoreceptors. Muscarinic cholinoreceptor antagonists block the effects of ACh at muscarinic cholinoreceptors in the parasympathetic autonomic nervous system and in the CNS. Nicotinic cholinoreceptor antagonists block the effects of ACh at ganglia of the parasympathetic and sympathetic nervous system (and medulla), and at the neuromuscular junction.

Structure

Like atropine, the prototype muscarinic cholinoreceptor antagonist **scopolamine is a tertiary amine.** As such, it has **ready access to the CNS** when administered parenterally, and it can be absorbed across the skin when combined with a suitable vehicle in a transdermal patch. **Quaternary amine antimuscarinic agents,** including **tiotropium bromide,** have **limited access to the CNS** and thus are used therapeutically for their peripheral effects.

Mechanism of Action

Interaction of scopolamine, atropine, or other antimuscarinic agents with muscarinic cholinoreceptors prevents the typical actions of ACh, such as activation of G-proteins and subsequent production of IP_3, and DAG that results in mobilization of calcium.

Administration

The patch formulation of scopolamine for motion sickness provides for up to 72 hours of pharmacologic activity. Scopolamine can also be administered IV, IM, or PO. Ipratropium bromide and tiotropium are administered topically to the airways as a metered-dose inhaler for COPD.

Pharmacokinetics

The duration of action of antimuscarinic agents ranges from less than a day (tropicamide) to 3–10 days (scopolamine, atropine).

COMPREHENSION QUESTIONS

3.1 Prescription of a muscarinic cholinoreceptor antagonist with a quaternary amine group is most appropriate for the patient with which of the following conditions?

A. A 50-year-old woman with angle-closure glaucoma
B. A 34-year-old man with gastrointestinal infectious enteritis
C. A 66-year-old man with mild dementia
D. A 56-year-old diabetic woman with urinary tract obstruction

3.2 A 16-year-old teenager is going on his first deep sea fishing trip and is using a scopolamine patch to ward off sea sickness. Which of the following is the most likely adverse effect he will experience?

A. Bradycardia
B. Drowsiness
C. Miosis
D. Urinary urgency

3.3 Cholinergic excess resulting from organophosphate insecticide poisoning can be treated with which of the following?

A. Atropine
B. Digoxin
C. Ipratropium bromide
D. Tropicamide

ANSWERS

3.1 **C.** Muscarinic cholinoreceptor antagonists with quaternary amine groups do not penetrate the CNS and are therefore unlikely to impair memory. By blocking gastrointestinal motility, these agents can cause increased retention of infecting organisms.

3.2 **B.** Scopolamine penetrates the CNS and can cause drowsiness and sedation. It also can cause mydriasis, tachycardia, and urinary retention.

3.3 **A.** Atropine is a tertiary amine that can penetrate the CNS. In addition to its peripheral blocking actions, it can also block the adverse CNS effects as a result of cholinergic excess. Tropicamide is also a tertiary amine. However, it has a very short duration of action and would be an unsuitable antidote. Ipratropium bromide is a charged quaternary ammonium compound that does not penetrate the CNS.

PHARMACOLOGY PEARLS

- Many antihistaminic agents, antipsychotic agents, and antidepressant agents have muscarinic cholinoreceptor antagonist (antimuscarinic) activity.
- Scopolamine is a tertiary amine and has ready access to the CNS when administered parenterally, whereas quaternary amine antimuscarinic agents, such as ipratropium bromide, have limited access to the CNS.
- Scopolamine can cause drowsiness and sedation, as well as mydriasis, tachycardia, and urinary retention.
- Cholinoreceptor agonists cause symptoms of SLUD—**s**alivation, **l**acrimation, **u**rination, **d**iarrhea—whereas cholinoreceptor antagonists have the opposite effects—dry mouth, dry eyes, urinary retention, constipation.

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CASE 4

A healthy 25-year-old man is undergoing a brief surgical procedure (inguinal hernia repair) requiring general anesthesia. Intubation and induction of anesthesia using IV succinylcholine and inhaled halothane proceed unremarkably. During surgery the patient develops muscle rigidity and tachycardia, and his temperature rapidly rises.

- What is the mechanism of action of succinylcholine?
- What reaction is occurring in the patient?
- What drug should immediately be given to the patient, and what is its mechanism of action?

ANSWERS TO CASE 4:
Skeletal Muscle Relaxants

Summary: A 25-year-old man develops muscle rigidity, tachycardia, and high fever during surgery.

- **Mechanism of action of succinylcholine:** Nicotinic receptor agonist at the motor endplate of the neuromuscular junction, which causes persistent stimulation and depolarization of muscle cells.
- **Reaction that is occurring:** Malignant hyperthermia.
- **Drug given for treatment and its mechanism of action:** Dantrolene, which acts by interfering with calcium release from the sarcoplasmic reticulum.

CLINICAL CORRELATION

Succinylcholine is the only depolarizing neuromuscular agent in wide clinical use. It is used for the rapid induction of a brief flaccid paralysis. It works as an agonist of the nicotinic receptor at the motor endplate of the neuromuscular junction. This causes a persistent stimulation and depolarization of the muscle, preventing stimulation of contraction by ACh. It has a rapid onset and short duration of action because it is quickly hydrolyzed by plasma and liver cholinesterase.

Malignant hyperthermia, a rare but significant cause of anesthetic morbidity and mortality, is an inherited **autosomal dominant disorder** that results in **tachycardia, muscle rigidity, and high body temperatures** in response to the use of certain **inhaled anesthetics** in combination with **muscle relaxants, usually succinylcholine.** It is caused by a **release of calcium ions from the sarcoplasmic reticulum in muscle cells. Dantrolene** interferes with this release and is therefore the treatment of choice for this condition.

APPROACH TO:
Pharmacology of Skeletal Muscle Relaxants

OBJECTIVES

1. Contrast the mechanism of action of depolarizing and nondepolarizing neuromuscular junction-blocking agents.
2. List the therapeutic uses and adverse effects of skeletal muscle relaxants.

DEFINITIONS

Hyperkalemia: Elevated levels of the electrolyte potassium in the serum.

Myalgia: Pain originating in skeletal muscle.

Depolarizing neuromuscular agent: A drug that acts at the neuromuscular junction to prevent the initiation of an action potential by ACh.

DISCUSSION

Class

Neuromuscular blocking agents are classified as either **depolarizing** or **nondepolarizing** (Table 4–1) and are used mostly as adjuncts with general anesthetics to block activity of ACh at the neuromuscular junction.

Succinylcholine is the prototype for **depolarizing agents** and used for **brief paralysis** for surgery and for intubation. **Tubocurarine,** the prototype, and other **nondepolarizing agents** (eg, cisatracurium, vecuronium, rocuronium) are used for **longer term paralysis** for surgery.

In addition to malignant hyperthermia, succinylcholine administration may result in **hyperkalemia,** particularly in patients with **burn and trauma,** which could result in **cardiac arrest.** Myalgia is also commonly reported. It is contraindicated in patients with neuromuscular disease, such as myasthenia gravis and muscular dystrophy, as well as in stroke. **Bradycardia** may also occur, but can be prevented by pretreatment with **atropine.**

Certain **nondepolarizing agents** may produce **hypotension,** as a result of histamine release and some ganglionic blocking activity, and tachycardia as a result of vagolytic activity. The effects of nondepolarizing agents may be reversed by the acetylcholinesterase inhibitor, neostigmine.

Numerous drug interactions between neuromuscular blocking agents and other drugs have been reported that lead to increased neuromuscular blockade, particularly with certain antibiotics and inhaled anesthetics.

Structure

The **neuromuscular blocking agents resemble ACh** (succinylcholine contains two linked ACh molecules) and contain **one or two quaternary nitrogens** that **limit entry into the CNS.**

Mechanism of Action

After a single dose, **succinylcholine occupies the nicotinic receptor** to produce a **persistent endplate depolarization** (phase I block) that results in flaccid paralysis because the muscles become unresponsive to endogenously released ACh. The initial depolarization is accompanied by muscle fasciculations. **Continued exposure of endplates to succinylcholine results in their repolarization.** However, through an

Table 4–1 • SELECTED SKELETAL MUSCLE RELAXANTS

Type of Agent	Mechanism of Action	Selected Adverse Effects
Depolarizing agents (succinylcholine)	Persistent endplate depolarization and desensitization	Malignant hyperthermia, hyperkalemia, myalgia
Nondepolarizing agents (tubocurarine, cisatracurium vecuronium, rocuronium)	Reversible competitive antagonists that block the action of ACh at nicotinic cholinoreceptor	Hypotension, tachycardia

unclear mechanism, they become relatively insensitive to subsequent depolarization (so-called desensitization, or phase II block).

Nondepolarizing blocking agents act as reversible competitive antagonists that block the action of ACh at nicotinic cholinoreceptors in muscle endplates and autonomic ganglia. In contrast to succinylcholine, which has a duration of action of about 6–10 min, the nondepolarizing agents have a longer duration of action (up to an hour).

Cholinesterase inhibitors (eg, neostigmine, pyridostigmine) can effectively **antagonize and reverse the neuromuscular blocking action of nondepolarizing agents and succinylcholine during phase II.** However, they will augment the action of succinylcholine during phase I.

Administration

The neuromuscular blocking agents are **highly polar** and therefore must be administered parenterally. Most nondepolarizing agents are eliminated through the kidney. Succinylcholine is eliminated by the hydrolytic action of plasma butyrylcholinesterase (pseudocholinesterase).

Pharmacokinetics

Neuromuscular blocking agents are **highly ionized** and therefore have limited volume of distribution and **limited access to the CNS.**

COMPREHENSION QUESTIONS

4.1 The use of succinylcholine as an adjunct to general anesthetics during surgery is based on its ability to:

A. Block the action of ACh at the motor endplate
B. Increase release of ACh from autonomic ganglia
C. Increase release of histamine from mast cells
D. Inhibit cholinesterase

4.2 Continued exposure of muscle endplates to succinylcholine results in their:

A. Conversion to ion channels
B. Enhanced sensitivity to ACh
C. Regeneration of ACh receptors
D. Repolarization

4.3 Cholinesterase inhibitors can reverse the action of which of the following?

A. Cisatracurium
B. Succinylcholine
C. Both A and B
D. Neither A nor B

4.4 A 35-year-old man undergoes surgery for a hernia repair. After the surgery, he complains of diffuse muscle aches, which the anesthesiologist states is likely caused by the skeletal muscle relaxant. He has a temperature of 37.8°C (100°F). Which of the following is the most accurate statement?

A. The agent also commonly causes hypokalemia.
B. The agent blocks ACh at the nicotinic receptor.
C. The agent causes persistent endplate depolarization and desensitization.
D. The patient likely has malignant hyperthermia.

ANSWERS

4.1 **A.** Succinylcholine acts like ACh to cause depolarization of the muscle endplate. However, unlike ACh, succinylcholine is not metabolized at the synapse. Therefore, the endplate remains depolarized and unresponsive to endogenous ACh, resulting in muscle paralysis.

4.2 **D.** Continued exposure of the muscle endplate to succinylcholine results in desensitization (phase II block) where the endplate repolarizes but cannot readily be depolarized.

4.3 **C.** Cholinesterase inhibitors like neostigmine can effectively antagonize and reverse the neuromuscular blocking action of nondepolarizing agents and succinylcholine during phase II. However, they will augment the action of succinylcholine during phase I.

4.4 **C.** Myalgia (muscle aches) is a common adverse reaction of depolarizing agents such as succinylcholine; these agents also may induce hyperkalemia and malignant hyperthermia.

PHARMACOLOGY PEARLS

- Malignant hyperthermia is a rare autosomal dominant disorder characterized by tachycardia, muscle rigidity, and high body temperatures, which occurs when the patient is exposed to inhaled anesthetics in combination with muscle relaxants, usually succinylcholine.
- Dantrolene interferes with the release of intracellular calcium and is therefore used to treat the muscle rigidity and hyperthermia associated with malignant hyperthermia.
- The neuromuscular blocking agents are highly polar and highly ionized and, therefore, must be administered parenterally and have limited volume of distribution and limited access to the CNS.
- A small number of patients (1:10,000) with atypical cholinesterase experience long-lasting apnea of 1–4 hours following succinylcholine (or the nondepolarizing neuromuscular blocking drug mivacurium that is also eliminated by the action of butyrylcholinesterase). Mechanical ventilation is used to manage the apnea even though prescreening could detect this rare condition.

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CASE 5

A 75-year-old woman with mild congestive heart failure is admitted to the intensive care unit (ICU) with sepsis caused by a urinary tract infection. She is hypotensive, with a blood pressure of 80/40 mm Hg, has an elevated heart rate (tachycardia) and decreased urine output (oliguria). Along with the institution of appropriate antibiotic therapy and IV fluids, a decision is made to start her on an IV infusion of norepinephrine to attempt to raise her blood pressure.

- What effects can be expected with norepinephrine?
- Which receptors mediate these effects?

ANSWERS TO CASE 5:
Sympathomimetic Agents

Summary: A 65-year-old woman in septic shock has persistent hypotension and oliguria requiring IV dopamine.

- **Effects of norepinephrine:** potent vasoconstriction.
- **Receptors involved:** α_1- and β_1-adrenoreceptors.

CLINICAL CORRELATION

Norepinephrine is a drug of choice in the treatment of septic shock, after fluid resuscitation has been optimized. Norepinephrine activates α_1- and β_1-adrenorecptors located in blood vessels and the heart, respectively, resulting in potent vasoconstriction. Although the action on β_1-adrenoreceptors would be expected to increase heart rate, a reflex bradycardia is produced due to increased blood pressure; the net effect is little to no change in heart rate. Volume resuscitation is required in any patient with volume depletion prior to or concomitant with vasoconstriction to assure adequate perfusion of tissues. Vasopressive agents are most commonly used in patients where fluid resuscitation is inadequate to restore blood pressure. Vasopressive agents are used in patients where aggressive fluid resuscitation is contraindicated, such as those with congestive heart failure, kidney failure, liver failure, or acute respiratory distress syndrome (ARDS); these patients risk development of pulmonary edema.

Although previously, dopamine was frequently used to treat this condition. The β_1-adrenoceptor-mediated effects in the heart result in an increase in cardiac output with minimal peripheral vasoconstriction. This contributes to dopamine's ability to raise systolic blood pressure with no effect or only a slight effect on diastolic pressure. Specific dopamine receptors in the vasculature of the renal, coronary, and splanchnic systems allow for reduced arterial resistance and increased blood flow. At higher doses, there is a peripheral α-adrenoceptor effect that overrides dopamine receptor-mediated vasodilation and results in vasoconstriction. The combination of renal blood-flow preservation, while supporting the blood pressure, is desirable in conditions of shock. This also contributes to increasing blood pressure. Prolonged high doses of dopamine can result in peripheral tissue necrosis because of the α-adrenoceptor-mediated vasoconstriction that reduces blood flow to the extremities, particularly in the digits.

APPROACH TO:

Pharmacology of Autonomic Sympathetic Agents

OBJECTIVES

1. Outline the effects of sympathomimetic agents on peripheral organ systems.
2. List the major sympathomimetic agonists and their routes of administration.
3. Describe the therapeutic and adverse effects of the major sympathomimetic drugs.

DEFINITIONS

Sympathomimetic agents: Drugs that either directly or indirectly mimic all or some of the effects of epinephrine or norepinephrine.

Receptor selectivity: Preferential binding (greater affinity) of a drug to a specific receptor group or receptor subtype at concentrations below which there is little, if any, interaction with another receptor group or subtype.

DISCUSSION

Class

Sympathomimetic agents act **directly** (eg, epinephrine, norepinephrine, dopamine, dobutamine, phenylephrine, metaraminol, methoxamine, albuterol, terbutaline) or indirectly, by causing the release of endogenous sympathetic agonists (amphetamine, ephedrine), to activate **α- and β-adrenoceptors**. Table 5–1 contrasts the effects of sympathetic adrenergic action with that of parasympathetic cholinergic activity in multiple organs.

Sympathomimetic agent adrenoceptor selectivity varies. Some are **nonselective** (eg, ephedrine), whereas some have greater affinity for α-adrenoceptors (eg, phenylephrine, metaraminol, methoxamine) or β_1-adrenoceptor (eg, dobutamine) or β_2-adrenoceptor (eg, terbutaline, albuterol) subgroups. However, selectivity is often lost as the dose of a sympathomimetic agent is increased. Compared to nonselective β-receptor agonists (isoproterenol), **β_1-selective sympathomimetic agents may increase cardiac output with minimal reflex tachycardia. α_2-Selective agents decrease blood pressure** by a presynaptic action in the CNS (clonidine, methyldopa).

The clinical utility of a particular sympathomimetic agent depends, among other factors, on the specific organ system and receptor subtypes that are involved.

In the **cardiovascular** system, a reduction in blood flow by relatively selective α-adrenoceptor sympathomimetic agents is used to achieve surgical hemostasis (epinephrine), reduced diffusion of local anesthetics (epinephrine), and a reduction of mucous membrane congestion in hay fever and for the common cold (ephedrine, phenylephrine). An increase in blood flow or blood pressure by α-adrenoceptor sympathomimetic agents is beneficial for the management of hypotensive

Table 5–1 • AUTONOMIC NERVOUS SYSTEM EFFECTS*

Organ	Sympathetic Adrenergic Receptor Action	Parasympathetic Cholinergic Receptor Action
Heart	β_1—increased heart rate and contractility	Decreased heart rate and contractility
Blood vessels†	α_1—constriction β_2—dilation	Dilation
Bronchi	β_2—bronchial smooth muscle relaxation	Bronchial smooth muscle contraction
GI tract	α_1—sphincter contraction β_2—relaxation	Overall contraction relaxation of sphincter
Kidney	β_1—renin release	No effect
Urinary bladder	α_1—sphincter contraction β_2—wall relaxation	Wall contraction sphincter relaxation
Adipose tissue Eye	β_1—increased lipolysis α_1—radial muscle contraction with pupil dilation	No effect Sphincter muscle contraction with pupil constriction ciliary muscle contraction

*See also Figure 1-1.
†No direct parasympathetic innervation.

emergencies (norepinephrine phenylephrine) and chronic orthostatic hypotension (oral ephedrine). Sympathomimetic agents such as epinephrine are also used for emergency short-term treatment of complete heart block and cardiac arrest.

Treatment of **bronchial asthma** represents a major use of **β_2-selective sympathomimetic agents** (eg, terbutaline, albuterol). Its effect is bronchodilation and relaxation of the smooth muscles of the bronchioles.

Ophthalmic examination is facilitated with the use of the **directly acting α-adrenoceptor sympathomimetic agonist,** phenylephrine. Apraclonidine (and the indirectly acting sympathomimetic agent, cocaine) is used to confirm the diagnosis of Horner syndrome. In addition to β-adrenoceptor-blocking agents, α_2-selective agents (eg, apraclonidine, brimonidine) are used to lower intraocular pressure in glaucoma.

The peripheral adverse effects of the sympathomimetic agents are generally an extension of their pharmacologic effects. These are most often cardiovascular in nature, particularly when they are administered parenterally, and may include increased blood pressure, arrhythmias, and cardiac failure.

Structure

Sympathomimetic agents, as well as norepinephrine and epinephrine, are **derived from phenylethylamine.** Substitutions on the amino group, the benzene ring or the α- or β-carbon, markedly alter the selectivity, activity, and metabolism of the sympathomimetic agents. For example, alkyl substitutions on the amino group tend to markedly increase β-adrenoceptor selectivity.

Mechanism of Action

Directly acting sympathomimetic agents bind to and activate adrenoceptors to mimic the actions of epinephrine or norepinephrine. Indirectly acting sympathomimetic agents mimic the actions of norepinephrine by either displacing it or inhibiting its reuptake from adrenergic nerve endings.

Administration

Sympathomimetic agents are available for administration by **topical, nasal, oral, ophthalmic, and parenteral routes** depending on the drug and condition being treated.

Pharmacokinetics

Like the catecholamines, norepinephrine and epinephrine, direct and indirect sympathomimetic agents may be subject to **metabolism and inactivation** by **COMT and MAO.** Phenylephrine is not metabolized by COMT.

COMPREHENSION QUESTIONS

5.1 A 25-year-old man is noted to be in septic shock due to ruptured appendicitis. IV norepinephrine is administered, and will likely result in which of the following?

A. Decrease cardiac output
B. Decrease systolic blood pressure
C. Increase renal blood flow
D. Produce significant peripheral vasoconstriction

5.2 Norepinephrine is metabolized by which of the following enzymes?

A. COMT
B. MAO
C. Both
D. Neither

5.3 Which of the following is the most accurate statement?

A. α-Adrenoceptor sympathomimetic agonists are used to reduce mucous membrane congestion.
B. α-Adrenoceptor agonists are used to treat bronchospasm.
C. β-Adrenoceptor agonists are used to reduce surgical bleeding.
D. β_2-Adrenoceptor agonist agents are used to prolong local anesthesia.

ANSWERS

5.1 **D.** Norepinephrine increases blood pressure by causing peripheral vasoconstriction by acting on α_1-adrenoreceptors.

5.2 **B.** Both COMT and MAO breakdown norepinephrine.

5.3 **A.** α-Adrenoceptor sympathomimetic agents will cause vasoconstriction and thereby reduce mucous membrane congestion.

PHARMACOLOGY PEARLS

- β_1-Selective sympathomimetic agents may increase cardiac output with minimal reflex tachycardia.
- α_2-Selective agents decrease blood pressure by a presynaptic action in the CNS.
- Terbutaline and albuterol are preferred over ephedrine for relieving the bronchoconstriction of asthma, and other bronchial conditions, because of their greater bronchiolar selectivity.

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CASE 6

A 70-year-old man is seen in follow-up at your office after he has been hospitalized for a myocardial infarction (MI). He underwent successful angioplasty and is currently asymptomatic. In the hospital, his blood pressure was consistently elevated. The patient's discharge medications include an ACE inhibitor, a statin, aspirin, and metoprolol.

- Metoprolol is selective for which adrenoceptor?
- What effects do agents such as metoprolol have on the cardiovascular system?
- In which organ is metoprolol primarily metabolized?

ANSWERS TO CASE 6:
Adrenoceptor Antagonists

Summary: A 70-year-old hypertensive man had a recent MI and is prescribed metoprolol.

- **Adrenoceptor selectively antagonized by metoprolol:** β_1.
- **Effect of β-adrenoceptor antagonists on the cardiovascular system:** Reduction of sympathetic-stimulated increases in heart rate, contractility, and cardiac output; lower blood pressure as a result of effects on the heart, renin-angiotensin system, and CNS; increased atrioventricular (AV) conduction time and refractoriness.
- **Organ in which metoprolol is metabolized:** Liver.

CLINICAL CORRELATION

β-Adrenergic receptor antagonists are widely used in medicine, primarily for their beneficial effects on the cardiovascular system and for lowering intraocular pressure in patients with glaucoma. Both the nonselective β-adrenoreceptor antagonists and the β_1-adrenoceptor selective antagonists are used to treat hypertension. The mechanism of their action is multifactorial, probably including reduction in cardiac output, reduction in renin release, and effects in the CNS. They are also beneficial for treating coronary artery disease. β-Blockers are part of the standard treatment after myocardial infarction as they reduce sympathetic-stimulated increases in heart rate and contractility. This helps to reduce myocardial oxygen demand, providing prophylaxis for angina. **β-Adrenoceptor antagonists have a proven benefit in prolonging survival after heart attacks.** They lengthen AV conduction time and refractoriness and suppress automaticity. This helps to prevent both supraventricular and ventricular arrhythmias.

APPROACH TO:
Pharmacology of Adrenoceptor Antagonists

OBJECTIVES

1. Describe the therapeutic uses and adverse effects of α-adrenoceptor antagonists.
2. Describe the therapeutic uses and adverse effects of β-adrenoceptor antagonists.
3. Contrast the differences between the nonselective and relatively β_1-selective adrenoceptor antagonists.

DEFINITIONS

Pheochromocytoma: A tumor of the adrenal medulla that releases excess levels of epinephrine and norepinephrine that can result in hypertension, cardiac anomalies, and severe headache.

Myocardial infarction: Death of cardiac muscle as a result of ischemia.

DISCUSSION

Class

There are two classes of clinically important α-adrenoceptor antagonists: nonselective antagonists and selective α_1-antagonists. **Phentolamine, a nonselective, competitive α-adrenoceptor antagonist,** and **phenoxybenzamine,** a **nonselective, noncompetitive α-adrenoceptor antagonist,** are used for the preoperative management of the marked catecholamine-induced **vasoconstriction** associated with **pheochromocytoma. Prazosin** and other **α_1-adrenoceptor selective antagonists** (doxazosin, terazosin) are used to manage **chronic mild-to-moderate hypertension** and **benign prostatic hypertrophy.**

In addition to the nonselective β-adrenoceptor antagonists, there are two classes of clinically important selective β-adrenoceptor antagonists, β_1 and β_2 (Table 6–1). The major clinical uses for β-adrenoceptor antagonists include ischemic heart disease, cardiac arrhythmias, hypertension, hyperthyroidism, and glaucoma. Ischemic heart disease is managed with nonselective β-adrenoceptor antagonists, propranolol, timolol, and nadolol, as well as β_1-adrenoceptor selective antagonists, metoprolol, atenolol, bisoprolol, nebivolol, and esmolol. **Cardiac arrhythmias** are managed, depending on the arrhythmia, with **propranolol and esmolol.**

Table 6–1 • β-ADRENOCEPTOR ANTAGONIST SELECTIVITY

Nonselective β-Adrenoceptor Antagonists
Propranol
Nadolol
Timolol
Selective β_1-Adrenoceptor Antagonists
Atenolol
Metoprolol
Esmolol
Nebivolol
Bisoprolol
Nonselective β- and α_1-Adrenoceptor Antagonists
Labetalol
Carvedilol

Although **hypertension** can be managed with a wide variety of **nonselective and β_1-adrenoceptor selective antagonists,** except esmolol, they are no longer considered the first-line drug for this indication. ACE inhibitors, Ca^{2+} channels blockers and thiazide diurectics are now considered the best drugs for treatment of hypertension. **Timolol** and other β-adrenoceptor antagonists are used to manage **glaucoma** by decreasing aqueous humor production and thereby reducing intraocular pressure.

Labetalol (and several other agents, including carvedilol), in formulations used clinically, **blocks both β- and α_1-adrenoceptors in a 3:1 ratio.** It also has some β_2-adrenoceptor agonist activity. Labetalol **lowers blood pressure** by **decreasing systemic vascular resistance** without any major effect on heart rate or cardiac output. It is used to treat hypertensive emergencies and hypertension from **pheochromocytoma.** Table 6–2 has a listing of selected drugs that affect autonomic function.

The **major adverse effects of nonselective α-adrenoceptor antagonists** are **cardiac stimulation,** primarily **tachycardia** because of baroreflex-mediated sympathetic discharge, and **postural hypotension.** Additional cardiac stimulation by phentolamine may be caused by antagonist activity at presynaptic α_2-adrenoceptors that result in increased norepinephrine release. (Prazosin and other selective α_1-adrenoceptor selective antagonists are less likely to cause reflex tachycardia.) A β-adrenoceptor antagonist may be required to counter the cardiac effects. α-Antagonists are rarely used as first-line agents for hypertension, as they are associated with a higher rate of congestive heart failure than other agents.

The **major adverse effects of nonselective β-adrenoceptor antagonists** are related to their effects on **smooth muscle, carbohydrate metabolism.** The use of a selective β-adrenoreceptor antagonists is recommended in patients with asthma or COPD. In patients, with **insulin-dependent diabetes, nonselective β-adrenoceptor antagonists** increase the incidence and severity of **hypoglycemic episodes.** The use of selective β_1-adrenoceptor antagonists in patients with this condition offers some potential benefits. β-Adrenoceptor antagonists can also cause erectile dysfunction. The β-adrenoreceptor antagonists can reduce HDL cholesterol and significantly raise serum triglercerides. The latter effect is particularly prevalent with the nonselective β-adrenoreceptor antagonists. Combined α- and β-adrenoreceptor antagonist (labetolol) or β-adrenoreceptor antagonists with sympathomimetic activity (acebutolol or pindolol) have no effect on serum tricglycerides.

Mechanism of Action

α-Adrenoceptor antagonists and β-adrenoceptor antagonists interact directly, and either competitively or irreversibly with, respectively, α-adrenoceptors and β-adrenoceptors to block actions of the endogenous catecholamines (norepinephrine and epinephrine), and exogenously administered sympathomimetic agents.

The α_1-adrenoreceptor is a G_i-coupled receptor whose activation leads to production of inositol triphosphate (IP_3) and diacylglycerol (DAG) to promote increased intracellular Ca^{2+} and ultimately smooth muscle contraction. Antagonists of this receptor will therefore promote smooth muscle relaxation; in blood vessels, where these receptors are largely expressed, this leads to dilation.

β-Adrenergic receptors are G_s-coupled receptors that activate adenylyl cyclase leading to elevation of cAMP and activation of protein kinase A. β_1-Adrenorecptors

Table 6–2 • SELECTED DRUGS AND THEIR EFFECTS ON THE AUTONOMIC NERVOUS SYSTEM

Drug	Adrenoceptor Activity	Mechanism of Action	Clinical Use
Epinephrine and other	Nonselective α- and β-adrenoceptor agonist	Bronchial smooth muscle dilation	Asthma allergic diseases to relax airways and reduce swelling
Phenylephrine	α_1-Adrenoreceptor stimulation	Vasoconstriction	Rhinitis and colds as decongestant
Albuterol	β_2-Adrenoceptor agonist	Bronchial smooth muscle dilation	Asthma
Propranolol	Nonselective β-adrenoceptor antagonist	Decreases heart rate, cardiac contractility	Hypertension, coronary heart disease, hyperthyroidism, migraine
Formoterol	β_2-Adrenoceptor agonist	Bronchial smooth muscle dilation	Asthma, COPD
Salmeterol	β_2-Adrenoceptor agonist	Bronchial smooth muscle dilation	Asthma, COPD
Phentolamine	Nonselective competitive α-adrenoceptor antagonist	Vasodilation	Preoperative management of the marked catecholamine-induced vasoconstriction associated with pheochromocytoma
Doxazosin	α_1-Adrenoreceptor selective antagonists	Vasodilation	Chronic mild to moderate hypertension and benign prostatic hypertrophy
Prazosin	α_1-Adrenoreceptor selective antagonists	Vasodilation	Chronic mild to moderate hypertension and benign prostatic hypertrophy
Terazosin	α_1-Adrenoreceptor selective antagonists	Vasodilation	Chronic mild to moderate hypertension and benign prostatic hypertrophy

are located primarily in the heart and kidney. In the heart, activation of β_1-receptors causes an increase in the force of contraction of cardiac muscle and an increase in heart rate. β_2-Adrenoreceptors are located in the bronchial, where their activation promotes relaxation. β_1-Antagonists, therefore, are effective in decreasing heart rate, contractility, and conduction velocity.

Administration

α- and β-adrenoceptor antagonists are administered orally or parenterally. β-Adrenoceptor antagonists are also available for ophthalmic application.

Pharmacokinetics

Metoprolol and propranolol undergo extensive and variable interindividual first-pass hepatic metabolism resulting in relatively low bioavailability. Oral sustained-release preparations of these agents are available. Drugs that inhibit cytochrome P450 2D6 may decrease the metabolism of carvedilol. Esmolol is ultra-short-acting as a result of its ester linkage that is rapidly metabolized by plasma esterases.

COMPREHENSION QUESTIONS

6.1 Which of the following actions of epinephrine are blocked by prazosin?

A. Bronchial dilation
B. Increased cardiac stroke volume
C. Increased heart rate
D. Mydriasis

6.2 A 34-year-old man is prescribed labetalol for hypertension. The effect on the cardiovascular system is a result of its action as an antagonist at which of the following?

A. α-Adrenoceptors
B. β-Adrenoceptors
C. Both α- and β-adrenoceptors
D. Muscarinic cholinoreceptors

6.3 Which of the following is the least likely clinical use for β-adrenoceptor antagonists?

A. Benign prostatic hypertrophy
B. Cardiac arrhythmias
C. Hypertension
D. Ischemic heart disease

6.4 Which of the following patients would not benefit from beta blockers?

A. 64-year-old female with daily migraines
B. 35-year-old female with hyperthyroidism and symptomatic tachycardia and tremors
C. 56-year-old male with erectile dysfunction
D. 74-year-old male with history of systolic heart failure that is stable
E. 57–year-old male with past history of coronary artery disease

ANSWERS

6.1 **D.** Prazosin is an α-adrenoceptor antagonist that will block epinephrine-mediated contraction of the radial smooth muscle of the eye that results in mydriasis. All the other actions listed are mediated by β-adrenoceptors, which would be blocked by β-adrenoceptor antagonists like propranolol.

6.2 **C.** Labetalol blocks both β- and α-adrenoceptors. It lowers blood pressure by decreasing systemic vascular resistance (α-adrenoceptor antagonist activity), without any major effect on heart rate or cardiac output (β-adrenoceptor antagonist activity).

6.3 **A.** β-Adrenoceptor antagonists are used therapeutically to manage ischemic heart disease, cardiac arrhythmias, and hypertension. α_1-Adrenoceptor selective antagonists are used to manage benign prostatic hypertrophy.

6.4 **C.** Beta blockers, especially at higher doses, will cause erectile dysfunction and hence it would not be ideal in this patient. Beta blockers have proven to reduce morbidity and mortality in patients with systolic, diastolic, and mixed dysfunction heart failure as well as in those with coronary artery disease. Propanalol is a first-line agent in migraine prophylaxis. It also is very effective in controlling the symptoms of tachycardia and tremors in Grave disease.

PHARMACOLOGY PEARLS

- α_1-Adrenoceptor selective antagonists, such as doxazosin and terazosin, are used for mild chronic hypertension and benign prostatic hypertrophy.
- The major clinical uses for β-adrenoceptor antagonists include ischemic heart disease, cardiac arrhythmias, hypertension, hyperthyroidism, and glaucoma.
- The **major adverse effects of nonselective β-adrenoceptor antagonists** are related to their effects on **bronchial smooth muscle** (increased airway resistance in asthmatics) and on **carbohydrate metabolism** (hypoglycemia in **insulin-dependent diabetics**).
- **β-Adrenoceptor antagonists** are no longer the first-line drug for the treatment of hypertension. ACE inhibitors, thiazide diurectics, and Ca^{2+} channels blockers are recommended.

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CASE 7

A 64-year-old female with a past medical history of coronary artery disease, hypertension, and congestive heart failure (CHF) presents with dyspnea at rest and with exertion, orthopnea, and lower extremity pitting edema. Her symptoms have worsened over the last 2 weeks and also include orthopnea, worsening exercise tolerance, and tachypnea. On examination, she is notably dyspneic and tachypneic, and also has jugular venous distension, 2+pitting edema, and rales on lung examination. Patient is also found to have an audible S3. Her chest x-ray, pro-Brain Natriuretic Peptide (BNP) level, and echocardiogram confirm the clinical suspicion of CHF exacerbation with pulmonary edema. She is already on maximal medical therapy with an ACE inhibitor, beta blocker, statin, and aspirin. She is appropriately placed on oxygen and given intravenous furosemide.

- What is the mechanism of action of furosemide?
- What electrolyte abnormalities can be caused by furosemide?

ANSWERS TO CASE 7:
Diuretics

Summary: A 64-year-old woman with pulmonary edema is prescribed furosemide.

- **Mechanism of action of furosemide:** Inhibit active NaCl reabsorption in the ascending limb of the loop of Henle, increasing water and electrolyte excretion.
- **Potential electrolyte abnormalities:** Hypokalemia, hypomagnesemia, and metabolic alkalosis because of enhanced H^+ excretion.

CLINICAL CORRELATION

Loop diuretics given intravenously promote diuresis within minutes, making them ideal for the treatment of acute pulmonary edema. Furosemide is the prototype and most widely used drug in this class. Loop diuretics inhibit NaCl reabsorption in the ascending limb of the loop of Henle. This causes a marked *increase* in the excretion of both water and electrolytes. **The excretion of potassium, magnesium, and calcium ions are all increased,** which may cause clinically significant adverse effects. A metabolic alkalosis may also occur as a result of the excretion of hydrogen ions. However, the ability to cause excretion of these electrolytes may also provide a clinical benefit in certain situations. **Forced diuresis by giving IV saline and furosemide is a primary method of treatment of hypercalcemia.**

APPROACH TO:
Pharmacology of the Loop Diuretics

OBJECTIVES

1. Know the site and mechanism of action of diuretic agents.
2. Know the electrolyte effects of the various diuretic agents.
3. Know the therapeutic uses, adverse effects, and contraindications to diuretic use.

DEFINITIONS

Diuretic: An agent that increases the production of urine. The most common are natriuretic diuretics, agents that increase urine production by interfering with sodium reabsorption in the kidney.

Edema: Accumulation of water in interstitial spaces. Causes include elevated blood pressure, a decrease in plasma oncotic pressure caused by a reduction in hepatic protein synthesis, or an increase in the oncotic pressure within the interstitial space.

DISCUSSION

Class

Natriuretic diuretics all act within the kidney to reduce the reabsorption of Na^+ and Cl^-. There are **four sites within the kidney** where various diuretics act; these correspond to four anatomic regions of the nephron. The **proximal tubule (site 1)** is the site of approximately 60 percent Na^+ reabsorption, but diuretics acting here are relatively ineffective because of the sodium-reabsorbing capacity in more distal regions of the nephron. The **ascending loop of Henle (site 2)** has active reabsorption of approximately 35 percent of the filtered Na^+. This is mediated by a cotransporter termed NKCC2 that transports 1 Na^+, 1 K^+, and 2 Cl^-. This is the molecular target of **furosemide** and other loop or "high-ceiling" diuretics. The **distal convoluted tubule (site 3)** is responsible for transport of approximately 15 percent of filtered sodium. **Thiazide** diuretics act in this segment of the nephron by interfering with a different cotransporter, NCC, which cotransports Na^+ and Cl^-. **Site 4 diuretics** act in the **collecting tubule** by interfering with Na^+ reabsorption through a specific channel, the epithelial sodium channel (ENaC), also called the amiloride-sensitive sodium channel (Figure 7–1).

Loop diuretics—furosemide, ethacrynic acid, bumetanide, and torsemide—are **highly acidic drugs** that act on the **luminal side of the tubule.** They reach this site by being secreted into the tubule by anion secretion in the proximal tubule. Compared with other diuretics, loop diuretics cause the greatest diuresis because the Na^+ K^- $2Cl^-$ transporter is responsible for a large fraction of Na^+ reabsorption, and regions distal to the ascending limb have more limited capacity for sodium transport. Loop diuretics are useful for the treatment of peripheral and pulmonary edema, which may occur secondarily as a consequence of cardiac failure, liver failure, or renal failure. Loop diuretics increase the excretion of Na^+, Cl^-, K^+, Mg^{2+}, Ca^{2+} and decrease the excretion of Li^+. The increased excretion of Ca^{2+} is clinically relevant, and loop diuretics can be used to treat hypercalcemia. Some of the diuretic actions of furosemide are mediated via prostaglandins, which have diuretic activity. Inhibitors of prostaglandin biosynthesis diminish the increase in diuresis produced by loop diuretics. In addition, furosemide has actions on the vascular system that occur prior to diuresis and this action may be mediated by prostaglandins. Other effects include changes in renal blood flow and a reduction in left-ventricular filling pressure. Loop diuretics increase urine production and decrease plasma K^+ in patients with acute renal failure.

The major adverse effects of loop diuretics are electrolyte imbalances. Increased delivery of Na^+ to the collecting duct increases K^+ and H^+ excretion. Loop diuretics therefore cause **hypokalemia, hypochloridemia, and metabolic alkalosis. Hyperuricemia** may be caused by the volume contraction and enhanced uric acid reabsorption by the proximal tubule. Loop diuretics can produce dose-dependent **ototoxicity** and this adverse effect is exacerbated in the presence of other ototoxic drugs such as the aminoglycosides.

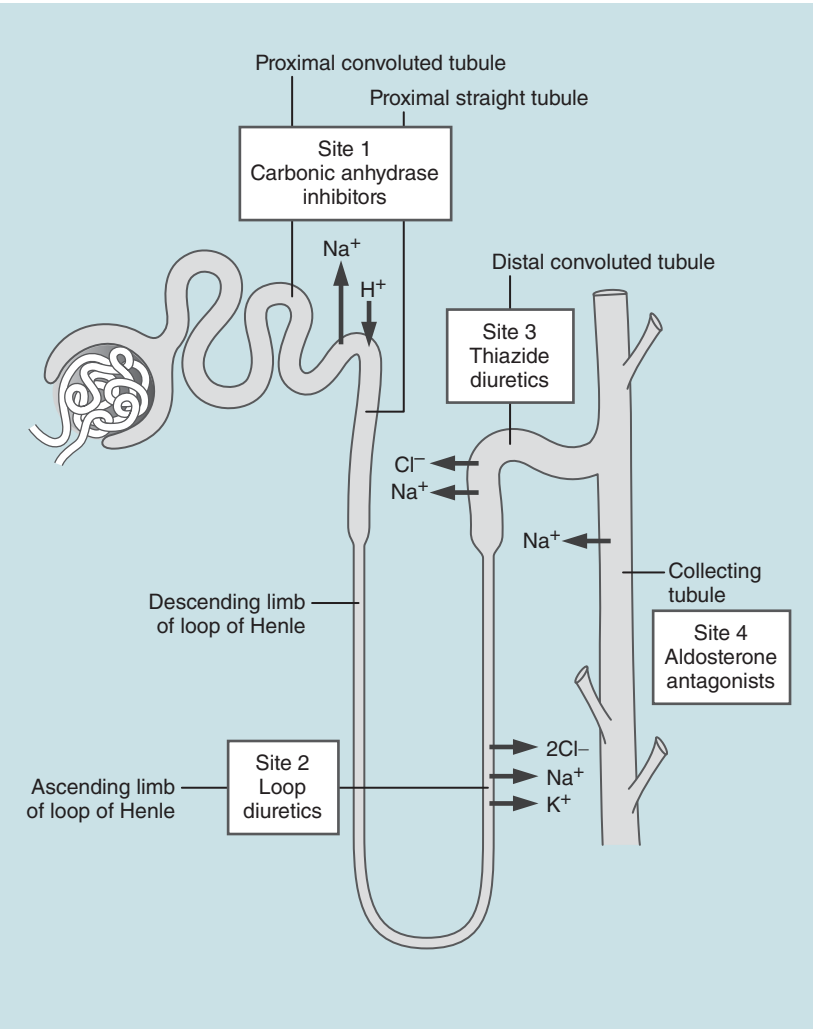

Figure 7–1. Sites of action of the nephron and diuretic agents.

Structure

Most loop diuretics are **sulfonamide derivatives;** the exceptions are ethacrynic acid, which is a phenoxyacetic acid derivative, and torsemide, which is a sulfonylurea. Due to the lack of a sulfur atom, ethacrynic acid causes fewer hypersensitivity reactions.

Mechanism of Action

The molecular target of furosemide and other loop or high-ceiling diuretics is the sodium-potassium-2 chloride cotransporter (NKCC2), which transports 1 Na^+, 1 K^+, and 2 Cl^-. The activity of this transporter is blocked by loop diuretics.

Administration

All loop diuretics can be administered orally, and their onset of action is approximately 1 hour (torsemide) to 2 hours (furosemide). Loop diuretics can also be administered IV, and for furosemide, this produces vasodilation in as little as 5 minutes and diuresis in 20 minutes.

Pharmacokinetics

All loop diuretics are extensively bound to plasma proteins. Half-lives vary from 45 minutes (bumetanide) to 3.5 hours (torsemide). Approximately 65 percent of a dose of furosemide is eliminated by the kidney, and the remainder is metabolized. Only 20 percent of torsemide is eliminated by the kidney, and 80 percent is metabolized.

COMPREHENSION QUESTIONS

7.1 Furosemide acts to inhibit Na^+ reabsorption in which of the following locations?

A. Ascending limb of the loop of Henle
B. Collecting duct
C. Descending limb of the loop of Henle
D. Distal convoluted tubule

7.2 A patient arrives in the emergency room in a coma and has a serum Ca^{2+} of 4.5 mM. You start a saline infusion of which of the following drugs?

A. Calcitonin
B. Ethacrynic acid
C. Hydrochlorothiazide
D. Spironolactone

7.3 A 55-year-old man with congestive heart failure is noted to be taking furosemide each day. Which of the following is most likely to be found in the serum?

A. Decreased potassium level
B. Decreased uric acid level
C. Elevated magnesium level
D. Low bicarbonate level

7.4 A 65-year-old male with CHF exacerbation is given IV furosemide. Which of the following adverse events are not associated with this medication?

A. Transient neurotoxicity from high dose
B. Hypotension
C. Worsening renal function
D. Hyperkalemia

ANSWERS

7.1 **A.** Furosemide acts specifically on a Na^+ K^+ $2Cl^-$ transporter in the ascending limb of the loop of Henle.

7.2 **B.** Loop diuretics such as ethacrynic acid increase the excretion of Ca^{2+}.

7.3 **A.** Furosemide leads to hypokalemia, hypomagnesemia, and metabolic alkylosis (elevated bicarbonate level).

7.4 **D.** Furosemide infusion may cause transient ototoxity with higher doses. Hypotension, hypokalemia, and azotemia with possible worsening renal failure are all possible adverse events with furosemide.

PHARMACOLOGY PEARLS

- Furosemide, which acts on the loop of Henle, is the most efficacious diuretic.
- Hypokalemia is a frequent adverse effect encountered with loop diuretics, and this can be managed with the concomitant use of potassium-sparing diuretics such as triamterene or spironolactone.
- Loop diuretics can produce dose-dependent ototoxicity; this is reduced with the non-sulfur containing ethacrynic acid.

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CASE 8

Following his third episode of gouty arthritis, a 50-year-old man sees you in the clinic. Each case was successfully treated acutely; however, your patient is interested in trying to prevent future episodes. He is not on regular medications and has a normal physical examination today. Blood work reveals an elevated serum uric acid level and otherwise normal renal function and electrolytes. A 24-hour urine collection for uric acid reveals that he is underexcreting uric acid. Suspecting that this is the cause of his recurrent gout, you place him on probenecid.

- What is the mechanism of action of probenecid?
- Which drugs could have their excretion inhibited by probenecid?

ANSWERS TO CASE 8:
Nondiuretic Inhibitors of Tubular Transport

Summary: A 50-year-old man with recurrent gout is prescribed probenecid.

- **Mechanism of action of probenecid:** Inhibits secretion of organic acids and decreases reabsorption of uric acid, causing a net increase in secretion.
- **Other drugs whose secretion could be inhibited:** Penicillin, indomethacin, and methotrexate.

CLINICAL CORRELATION

Gout is a disease in which uric acid crystals deposit in joints, causing an extremely painful acute inflammatory arthritis. Persons with recurrent gout often have chronically elevated levels of uric acid in their blood. This hyperuricemia is frequently caused by either overproduction of uric acid or underexcretion of uric acid by the kidneys. Probenecid (and other uricosuric drugs) promotes the excretion of uric acid. It works by inhibiting the secretion of organic acids from the plasma into the tubular lumen and blocking the reuptake of uric acid. The net result of this is an **increase in the excretion of uric acid.** The benefit of this is the prevention of recurrent gout attacks in chronic underexcreters of uric acid. In those individuals who overproduce uric acid, **allopurinol** or **febuxostat** is used. These drugs inhibit xanthine oxidase, a key enzyme in the production of uric acid. For patients with severe gout refractory to the above drugs, IV infusion of pegloticase can quickly reduce serum urate and reduce deposits in joints.

APPROACH TO:
Pharmacology of Uricosuric Agents

OBJECTIVES

1. Understand the mechanism of action of uricosuric agents.
2. Know the therapeutic uses, adverse effects, and contraindications to uricosurics.
3. Know the mechanism of action and use of allopurinol.

DEFINITIONS

Uricosuric agents: Increase the mass of uric acid that is excreted in the urine.

Renal secretion: Moves solutes such as urate from the plasma into the urine.

Renal reabsorption: Moves solutes from the urine back into the plasma.

DISCUSSION

Class

Urate is both secreted and reabsorbed by several independent molecular transporters located in the proximal tubule. Urate is nearly completely secreted into the lumen of the nephron against an electrochemical gradient by the action of **organic acid transporter-1 (OAT-1) and organic acid transporter-3 (OAT-3).** These cotransporters exchange α-ketoglutarate and urate (or other organic anions) and move urate from the plasma into the tubular cell. The protein UAT is an electrically neutral channel that permits uric acid to leave tubular cells and enter either the tubular lumen or the plasma. URAT1, located on the apical membrane of tubular cells, is thought to be responsible for most of the reabsorption of urate from the filtrate. URAT1 is a transporter that is capable of exchanging a variety of anions with urate in an electrically neutral manner. Interaction of uricosuric agents such as probenecid with URAT1 diminishes the reabsorption of urate and increases urate excretion. All of these transporters or channels are relatively nonselective with respect to the organic acid transported. OAT-1 and OAT-3 are capable of secreting most organic acids including probenecid, penicillin, aspirin, furosemide, and hydrochlorothiazide.

In patients with **gout, probenecid can be used prophylactically; uricosuric drugs will not diminish the severity of an acute attack.** An **acute gouty attack** may be **precipitated** by the **initiation of probenecid treatment** as uric acid is mobilized out of joints. **Adequate hydration** should be ensured, because probenecid predisposes patients to the formation of **uric acid kidney stones.**

Probenecid is also useful for decreasing the excretion of penicillin, because **penicillin is eliminated** primarily by renal secretion mediated by **OAT-1 and OAT-3.** Probenecid competes for this secretion and thereby reduces the rate of elimination and **increases both the biological half-life of penicillin and the plasma concentration** of the antibiotic more than twofold. This adjunct use of probenecid is particularly useful in single-dose regimens for the treatment of gonococcal infections with long-acting penicillins such as penicillin G.

Secretion of organic acids is quite nonspecific, and most acidic drugs are secreted by the same transporters OAT-1 and OAT-3. This implies that nearly any combination of acidic drugs will compete for elimination at the level of the transporters, and the effects on elimination of each individual drug must be considered. For example, the half-life of diuretics such as furosemide will be increased by probenecid, and this may require dosage adjustment. **Aspirin,** another acidic drug, **will compete with probenecid for secretion.** This reduces the action of probenecid to increase uric acid excretion and thus increases plasma urate. Therefore, **aspirin is contraindicated in patients with gout who are taking probenecid.**

The most common adverse effect of probenecid is gastrointestinal (GI) upset, and approximately 2 percent of patients experience a hypersensitivity reaction usually manifest as a skin rash. The incidence of hypersensitivity is lower with sulfinpyrazone, but the incidence of GI upset is higher.

The alternate therapeutic approach to the treatment of gout is to reduce the **production of uric acid with an inhibitor of the enzyme xanthine oxidase.** This enzyme produces uric acid in a two-step reaction from the purine hypoxanthine.

Allopurinol and **febuxostat** are drugs used to inhibit xanthine oxidase. Allopurinol is metabolized to alloxanthine by xanthine oxidase, and this metabolite is a long-lasting inhibitor of the enzyme. Febuxostat is a more specific inhibitor of xanthine oxidase than allopurinol.

Uric acid accumulates in humans because we lack the enzyme uricase, which converts urate to the water-soluble allantoin. Recombinant uricase is available as **pegloticase,** which is administered by infusion. Pegloticase is used in severe refractory gout.

Structure

Probenecid is a lipid-soluble benzoic acid derivative with a pKa of 3.4. Another agent in this class is sulfinpyrazone, a pyrazolone derivative similar to the anti-inflammatory agent phenylbutazone. It has a pKa of 2.8 but is no longer marketed in the United States.

Mechanism of Action

Both probenecid and sulfinpyrazone are secreted into the lumen of the nephron via OAT-1 and OAT-3 where the drugs can diminish the ability of URAT1 to reabsorb urate.

Administration

Both drugs are active orally, and both are nearly completely absorbed.

Pharmacokinetics

The half-life of probenecid is 5–8 hours; sulfinpyrazone is approximately 3 hours, but its uricosuric actions can last as long as 10 hours. Increased excretion of uric acid occurs promptly after oral administration. Both agents are eliminated in the urine.

COMPREHENSION QUESTIONS

8.1 Probenecid is effective in treating gout because it decreases which of the following?

A. Inflammation in affected joints
B. Production of uric acid
C. Reabsorption of uric acid
D. Secretion of uric acid

8.2 Which of the following describes the action of allopurinol?

A. Inhibits metabolism of purines to uric acid
B. Inhibits prostaglandin biosynthesis
C. Inhibits uric acid reabsorption
D. Interferes with cytokine production

8.3 An 18-year-old man who is known to have non-penicillinase-producing gonococcal urethritis is given an injection of penicillin and probenecid. What is the mechanism used by probenecid that makes penicillin more efficacious?

A. Decreases the bacterial resistance by inhibiting penicillinase production

B. Increases the half-life and serum level by decreasing the renal excretion of penicillin

C. Prolongs the duration of action by affecting the liver metabolism of penicillin

D. Promotes entry of the penicillin into the bacteria

ANSWERS

8.1 **C.** Probenecid does inhibit renal tubular secretion of urate, but at therapeutic doses it inhibits reabsorption to a greater degree, thereby increasing net excretion urate.

8.2 **A.** Allopurinol interferes with the metabolism of purines by inhibiting the enzyme xanthine oxidase.

8.3 **B.** Probenecid decreases the renal excretion of penicillin, thereby increasing both the half-life and the serum level.

PHARMACOLOGY PEARLS

- At low doses, probenecid inhibition of urate secretion predominates, and this paradoxically increases plasma urate.
- At higher doses, inhibition of reabsorption predominates, leading to the therapeutically useful **increased** excretion of urate.
- An acute gouty attack may be precipitated by the initiation of probenecid treatment as uric acid is mobilized out of joints.
- Probenecid is also useful for decreasing the excretion of penicillin and cephalosporins.
- Patients are typically begun on a high loading dose to ensure the action on reabsorption is achieved.
- Keeping serum uric acid levels <6.0 have been shown to prevent recurrent gout attacks.
- Pegloticase is used for severe drug-refractory gout.

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CASE 9

A 72-year-old man presents to the office for routine follow-up. He is under treatment for hypertension and congestive heart failure with enalapril and a diuretic. His blood pressure is under acceptable control, and he has no symptoms of heart failure at present. He does complain that he has been coughing frequently in the past few months. History and examination reveal no other cause of a chronic cough, so you decide to discontinue his enalapril and start him on losartan.

- What is the mechanism of action of enalapril?
- By what mechanism does enalapril convert to its active form enalaprilat?
- What is the likely cause of the cough?
- What is the mechanism of action of losartan?

ANSWERS TO CASE 9:
Drugs Active on the Renin-Angiotensin System

Summary: A 72-year-old man with hypertension and congestive heart failure presents with an ACE inhibitor-induced cough, and is switched to losartan.

- **Mechanism of action of enalapril:** Inhibits the conversion of angiotensin I to angiotensin II; this also inhibits the angiotensin II-stimulated release of aldosterone. Angiotensin-converting enzyme (ACE) inhibitors also reduce the **inactivation of bradykinin.**
- **Mechanism of converting enalapril to enalaprilat:** Deesterification in the liver.
- **Mechanism of ACE inhibitor-induced cough:** Secondary to the increased bradykinin levels, which is caused by reduction in the inactivation of bradykinin.
- **Mechanism of action of angiotensin receptor blockers (ARBs):** Antagonists of angiotensin-1 (AT-1) receptors, which mediate the pressor effects of angiotensin II.

CLINICAL CORRELATION

ACE inhibitors have gained wide-scale use in medicine for their effectiveness in hypertension, congestive heart failure, coronary artery disease, and renal protection in diabetics. They inhibit the conversion of angiotensin I to angiotensin II. Angiotensin II is a *potent* vasoconstrictor and also stimulates the release of aldosterone, which promotes sodium and water retention. Angiotensin II also increases catecholamine release by the adrenal medulla and at sympathetic nerves. *Inhibition of the production of angiotensin II* reduces vascular resistance and sodium and water retention. Another effect of ACE inhibitors is to reduce the inactivation of bradykinin. Active bradykinin is a vasodilator, and inhibiting its degradation provides an additive mechanism to lower blood pressure. However, raising bradykinin levels contributes to one of the ACE inhibitors' most bothersome side effects, chronic dry cough. Elevated bradykinin can also cause angioedema. In general the drugs are well tolerated, but along with cough, can cause hyperkalemia and should be used with caution with potassium-sparing diuretics or in persons with impaired renal function. **ARBs** are antagonists of the angiotensin I receptor, which mediates the direct vasoconstrictor effect of angiotensin II. This also blocks the release of aldosterone. ARBs have a much reduced effect on the bradykinin system and have a much lower incidence of cough and angioedema. ARBs rarely cause chronic cough. They are also well tolerated but, like ACE inhibitors, can cause hyperkalemia. **Aliskiren** (Tekturna) is a small-molecule direct renin inhibitor. It appears to be as efficacious as ACE inhibitors or ARBs, but clinical experience is more limited.

APPROACH TO:

Pharmacology Of The Renin-Angiotensin System

OBJECTIVES

1. Know the mechanism of action of ACE inhibitors.
2. Know the therapeutic uses, side effects, and contraindications to ACE inhibitor use.
3. Know the mechanism of action of ARBs.
4. Know the therapeutic uses, side effects, and contraindications to ARB use.

DEFINITIONS

Hypertension: From the Seventh Report, Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure, normal blood pressure is 120/80 mm Hg. Progressive disease may be staged as prehypertensive (120–139/80–89), Stage 1 (140–159/90–99), and Stage2 (>160/>100).

Bradykinin: A member of a class of peptides, the kinins, that have a variety of effects on the cardiovascular system, including vasodilatation and inflammation.

ARB: Angiotensin receptor blocker, more precisely angiotensin AT-1 receptor blockers.

DISCUSSION

Class

The **renin-angiotensin-aldosterone system provides a humoral system for controlling blood pressure and electrolyte levels.** The "sensors" in this **system monitor Na^+, K^+, vascular volume, and blood pressure.** A reduction in blood pressure, detected by intrarenal stretch receptors, or a fall in the delivery of Na^+ to the distal portions of the nephron results in release of renin from the juxtaglomerular apparatus (JGA). Renin secretion can also be increased through the baroreceptor reflex mediated by increased central nervous system (CNS) outflow and β_1-adrenergic receptors on the JGA. Renin is an aspartyl protease that cleaves angiotensinogen, a 56-kD polypeptide produced in the liver, to the decapeptide angiotensin I (Figure 9–1, "classic" pathway).

Angiotensin I is biologically inactive and is **rapidly converted to the octapeptide angiotensin II** by the action of **ACE,** a dipeptidyl peptidase. ACE is also responsible for degradation of bradykinin. ACE2 is a unique gene product that is 41 percent identical to ACE. It cleaves angiotensin II (Ang 1–8) into angiotensin 1–7.

Metabolism of Angiotensinogen

The "classic" pathway consists of angiotensinogen, which is cleaved by renin to AgI, which in turn is cleaved by ACE to AgII. AgII binds to AT-1 and AT-2 receptors. AgI or AgII can be cleaved by the carboxypeptidase ACE2 to AgI-7. AgI-7 binds to

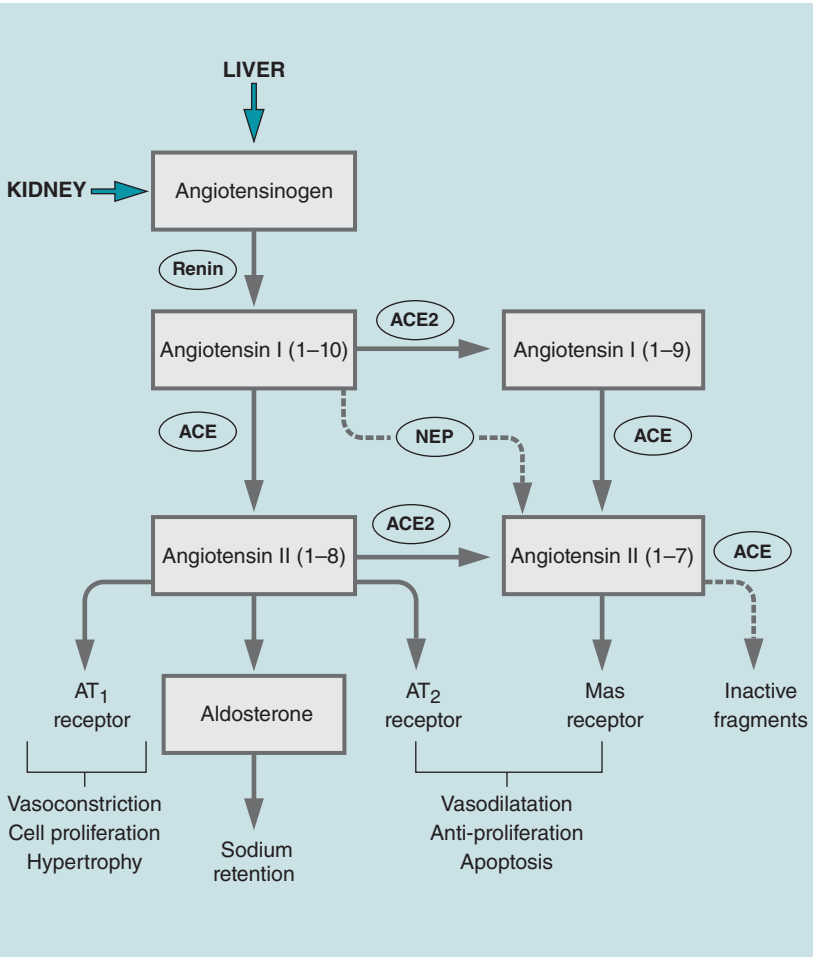

Figure 9–1. Schematic of angiotensin pathway.

the Mas receptor whose actions oppose those of AT-1 receptors. AgI-7 can also be formed by neprilysin (NEP), an endopeptidase that cleaves a number of physiologically important substrates. AgI-7 has physiologic actions that oppose those of AgII, including vasodilatation and antiproliferative effects.

Angiotensin II has multiple actions that act in concert to increase blood pressure and alter electrolyte levels. **Angiotensin II is a potent vasoconstrictor,** 10–40 times more potent than epinephrine, an effect **mediated by receptor-coupled Ca^{2+} channels** in **vascular smooth muscle cells,** as described below. **Angiotensin II enhances the release of catecholamines** both from the adrenal medulla and at peripheral nerve endings. Within the adrenal cortex, **angiotensin II increases the biosynthesis of aldosterone**, which leads to an increase in Na^+ and water reabsorption in the kidneys and volume expansion. Angiotensin II has several actions within the

CNS, including altering vagal tone to increase blood pressure, increasing thirst, and increasing the release of antidiuretic hormone.

Angiotensin II also has effects on the heart and the vasculature that do not directly affect blood pressure. **Angiotensin II induces cardiac hypertrophy,** is proproliferative, and enhances matrix remodeling and the deposition of matrix proteins, which leads to **increased myocardial stiffness.** Within vessel walls, angiotensin II is proinflammatory and can stimulate the release of several chemokines.

Three angiotensin receptors mediate these actions. The AT-1 and angiotensin-2 (AT-2) receptors have been described in various tissues. Both are seven-transmembrane receptors that appear to couple to various signaling pathways. AT-1 receptors bind angiotensin II, angiotensin III, and angiotensin IV. This receptor mediates most of the cardiovascular and central responses to angiotensin II, including vasoconstriction of vascular smooth muscle and aldosterone biosynthesis in the adrenal medulla. AT-1 receptors also mediate the cardiac hypertrophic and proproliferative responses to angiotensin II. AT-2 receptors also bind angiotensin II and play a role in the development of the cardiovascular system. In general, activation of AT-2 receptors is physiologically antagonistic to the action of AT-1 receptors. Activation of AT-2 receptors is hypotensive and antiproliferative and is coupled to distinctly different signaling pathways compared to AT-1 receptors. Angiotensin-4 (AT-4) receptors appear to be identical to transmembrane aminopeptidase insulin-regulated aminopeptidase (IRAP) and have a single transmembrane domain. AT-4 receptors are expressed in the numerous tissues and bind angiotensin IV. Activation of these receptors has been reported to regulate cerebral blood flow, and to stimulate endothelial cell expression of plasminogen activator inhibitor, and has effects on both memory and learning.

AgI-7 is produced by the action of ACE2. AgI-7 binds to the Mas receptor, another G-protein-coupled receptor. AgI-7 has numerous beneficial cardiovascular actions, including antihypertensive, antifibrotic, antioxidant, anti-inflammatory, and antiatherosclerotic effects.

Inhibition of the renin-angiotension system (RAS) is accomplished pharmacologically in three ways: inhibition of the production of angiotensin II, blockade of AT-1 receptors, or inhibition of renin activity. **ACE inhibitors**, or peptidyl dipeptidase (PDP) inhibitors, include **enalapril, lisinopril, fosinopril, captopril,** and nine others. These drugs differ in their chemistry and pharmacokinetic properties, but all are orally active, have the same range of activities, and are equally effective clinically. **ACE is the enzyme responsible for both *activation* of angiotensin I (metabolism to angiotensin II) and *inactivation* of bradykinin.** The decreased metabolism of bradykinin is partly responsible for the hypotensive action of ACE inhibitors, and is also responsible for enhancing the irritability of airways that leads to the **dry cough** associated with ACE inhibitors and seen in 10–33 percent of patients taking the drugs. Elevated bradykinin is also associated with angioedema (0.1–0.5% incidence).

ARBs block the action of angiotensin II by acting as antagonists at AT-1 receptors. These nonpeptide antagonists include **losartan, valsartan, candesartan,** and five others. ARBs bind with high affinity to AT-1 receptors without interfering with AT-2 or AT-4 receptors.

The **ACE inhibitors and ARBs are equally effective in reducing blood pressure.** More clinical experience exists with the ACE inhibitors, and it has been well established that this class of drugs reduces the risk of second events in patients who have had an MI and renal damage in patients with diabetic nephropathy. **Hypotension and hyperkalemia are adverse effects seen with both classes of RAS inhibitors. Cough and angioedema, caused by increased bradykinin** levels, are more frequently seen with the **ACE inhibitors. ARBs** have been shown to have anti-inflammatory activity and can decrease the production of several cytokines. This activity appears to be independent of AT-1 receptor blockade.

Aliskiren is a small molecule inhibitor of renin and is approved for use as an antihypertensive. Several clinical trials have shown aliskiren as effective in 24-hour blood pressure control as ARBs with a similar safety and tolerability profile. Aliskiren was shown to be more effective than hydrochlorothiazide in hypertensive obese patients.

Structure

Although the various ACE inhibitors have different chemical structures, they are mostly based on extensive modifications of L-proline. The ARBs are also quite distinct chemically: Valsartan is an L-valine derivative, and losartan is an imidazole derivative. Aliskiren was designed based on the crystal structure of renin and is a nonpeptide, small molecule, transition-state mimetic that binds to the active site of the enzyme and is effective in the nM range.

Mechanism of Action

ACE inhibitors are all competitive inhibitors of angiotensin-converting enzyme. ARBs are competitive antagonists of the angiotensin II type 1 receptor (AT-1), while aliskiren is a direct renin inhibitor.

Administration

All ACE inhibitors are available for oral administration. Enalaprilat, the active metabolite of enalapril, is available for intravenous infusion. Aliskiren is an oral agent. Coadministration of ARBs and ACE inhibitors, while demonstrating additive reductions in blood pressure, may be associated with increased frequency of renal dysfunction. Combinations of aliskiren with an ARB, a thiazide, a calcium channel blocker, or atenolol have all shown a greater reduction in blood pressure compared to monotherapy.

Pharmacokinetics

Many of the current ACE inhibitors are prodrugs and require conversion to the active metabolite in the liver. For example, enalapril is converted to enalaprilat, and fosinopril is converted into fosinoprilat. Captopril and lisinopril are active drugs that do not require metabolism. The onset of action of ACE inhibitors is 0.5–2 hours, and the duration of action is typically 24 hours (captopril is 6 hours). Most are eliminated in the urine. Aliskiren is poorly absorbed (2–3%) and is eliminated unchanged by the hepatobiliary system.

COMPREHENSION QUESTIONS

9.1 Losartan acts to decrease which of the following?

A. AT-1 receptor activity
B. Bradykinin production
C. Production of angiotensin II
D. Renin production

9.2 Which of the following is a limiting adverse effect of ACE inhibitors?

A. Acidosis
B. Hyperkalemia
C. Hypernatremia
D. Hypokalemia
E. Hyponatremia

9.3 Which of the following is an advantage of losartan over enalapril?

A. Better efficacy in lower blood pressure
B. Better prevention of secondary myocardial events
C. Less cost
D. Less incidence of angioedema

9.4 A 74-year-old male with PMH CHF, prior MI, CKD Stage 3, diabetes is being treated with an ACE inhibitor (among other medications). Which of the following conditions does the ACE inhibitor offer proven benefit?

A. CHF
B. CAD
C. CKD
D. DMII
E. All of the above

ANSWERS

9.1 **A.** Losartan is a prototypical angiotensin AT-1 receptor antagonist.

9.2 **B.** By reducing aldosterone levels, ACE inhibitors decrease K^+ excretion in the distal nephron.

9.3 **D.** Losartan does not lead to elevated bradykinin levels; thus, there is less of an incidence of angioedema and dry cough. The effects on blood pressure are equal. The track record for prevention of secondary cardiovascular events is well established for ACE inhibitors, although the same is speculated for ARBs.

9.4 **E.** ACE inhibitors and ARBs have been shown in numerous trials to improve outcomes in cardiovascular disease such as CAD/CHF by optimizing preload, reducing afterload, decreasing remodeling, and controlling blood pressure. They have also been proven in reducing proteinuria and being renoprotective in CKD and diabetic patients.

PHARMACOLOGY PEARLS

- Elevation of the bradykinin levels is thought to be the etiology of the dry cough and angioedema of ACE inhibitors.
- ACE inhibitors improve outcome in patients with cardiovascular disease and have been recommended as therapy in several guidelines.
- Clinical experience suggests that inhibitors of the renin-angiotensin system are somewhat less effective in African Americans.
- ARBs block the action of angiotensin II by acting as antagonists at AT-1 receptors.

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CASE 10

A 69-year-old male with a past medical history of congestive heart failure, type II diabetes mellitus, hypertension, and coronary artery disease presents for follow-up. Patient has had several MIs, a depressed ejection fraction (EF), and worsening heart failure—symptoms of dyspnea, orthopnea, paroxysmal nocturnal dyspnea, and edema despite maximal ACE inhibitor, beta blocker, and diuretic use. Patient's diabetes is well controlled and he has a normal renal function. You decide to add digoxin for symptomatic relief.

- What is the effect of digoxin on the normal heart?
- What is the effect of digoxin on the failing heart?
- What neural effects does digoxin have?
- What are the side effects and toxicities of digoxin?

ANSWERS TO CASE 10:

Agents Used to Treat Congestive Heart Failure

Summary: A 69-year-old man with congestive heart failure, hypertension, and diabetes mellitus has a markedly low EF and is prescribed digoxin.

- **Effect on a normal heart:** Increased systemic vascular resistance and constriction of smooth muscle in veins, which may decrease cardiac output.
- **Effect on a failing heart:** Increased stroke volume and increased cardiac output.
- **Neural effects:** Decreased sympathetic tone and increased vagal activity, resulting in inhibition of sinoatrial (SA) node and delayed conduction through atrioventricular (AV) node.
- **Side effects and toxicities:** Induction of arrhythmias, loss of appetite, nausea, vomiting, diarrhea, disorientation, generalized fatigue, and visual disturbances.

CLINICAL CORRELATION

Digoxin can be useful in improving some of the symptoms of congestive heart failure, but its use must be closely monitored. Digoxin works by inhibiting the sodium-potassium adenosine triphosphatase (ATPase), primarily in cardiac muscle cells. This causes increased intracellular sodium and decreased intracellular potassium. The increased intracellular sodium reduces the exchange of intracellular calcium for extracellular sodium, causing an **increased intracellular calcium level**. The overall effect of this is to allow for a greater release of calcium with each action potential. This has a positive inotropic effect. In a failing heart, stroke volume and cardiac output are increased. End-diastolic volume, venous pressure, and blood volume are decreased. These circulatory improvements also result in a reduction of sympathetic tone. This further improves circulation by lowering systemic vascular resistance. **Digoxin also has the effect of increasing vagal activity,** which inhibits the SA node and slows conduction through the AV node. This is beneficial in patients with atrial tachyarrhythmias such as atrial fibrillation, atrial flutter, and atrial tachycardias. **Digoxin has a narrow therapeutic index,** and its **level in the blood must be closely monitored.** The **dose must be adjusted for renal impairment,** because it is cleared by the kidney. Toxic digoxin levels may produce many types of **arrhythmias,** with **AV blocks and bradycardia** being common. Mental status changes and gastrointestinal symptoms are common as well. Asymptomatic elevations in digoxin levels are usually treated by discontinuing or reducing the drug's dosage. Symptomatic toxicity, particularly arrhythmias, is **most often treated by the IV infusion of digoxin-binding antibodies.**

APPROACH TO:

Pharmacology of the Cardiac Glycosides

OBJECTIVES

1. Know the mechanism of action of the cardiac glycosides.
2. Know the therapeutic uses, adverse effects, and toxicities of cardiac glycosides.
3. Know the other agents used frequently in the treatment of congestive heart failure.

DEFINITIONS

Cardiac glycosides: The cardenolides include digitalis, digoxin, digitoxin, and ouabain. Digoxin is the only preparation approved in the United States.

Inotropic: Affecting myocardial contractility.

Chronotropic: Affecting heart rate.

Congestive heart failure: A syndrome with multiple causes that may affect either systole or diastole. Left heart failure leads to pulmonary congestion and reduced cardiac output and appears in patients with MI, aortic and mitral valve disease, and hypertension. Right heart failure leads to peripheral edema and ascites and appears in patients with tricuspid valve disease, cor pulmonale, and prolonged left heart failure. The New York Heart Association classification of congestive heart failure includes class I (mild disease) to class IV (severe disease).

DISCUSSION

Class

The medicinal actions of the cardiac glycosides, digitalis, have been used successfully for over 200 years, and they have both positive inotropic and antiarrhythmic properties. **Digoxin is the most commonly used cardiac glycoside. Cardiac glycosides act to indirectly increase intracellular calcium** (Figure 10–1). **Digitalis binds to a specific site on the outside of the Na^+/K^+-ATPase** and this reduces the activity of the enzyme. All cells express Na^+/K^+-ATPase, but there are several different isoforms of the enzyme; the isoforms expressed by **cardiac myocytes and vagal neurons are the most susceptible to digitalis.** Inhibition of the enzyme by digitalis causes an increase in intracellular Na^+ and decreases the Na^+ concentration gradient across the plasma membrane. It is this Na^+ concentration that provides the driving force for the Na^+-Ca^{2+} antiporter. The rate of transport of Ca^{2+} out of the cell is reduced, and this leads to an increase in intracellular Ca^{2+}, greater activation of contractile elements, and an increase in the force of contraction of the heart. The **electrical characteristics of myocardial cells** are also **altered** by the **cardiac glycosides.** The most important effect is a **shortening of the action potential** that produces a **shortening of both atrial and ventricular refractoriness.** There is also an **increase in the automaticity of the heart,** both within the AV node and in the cardiac myocytes.

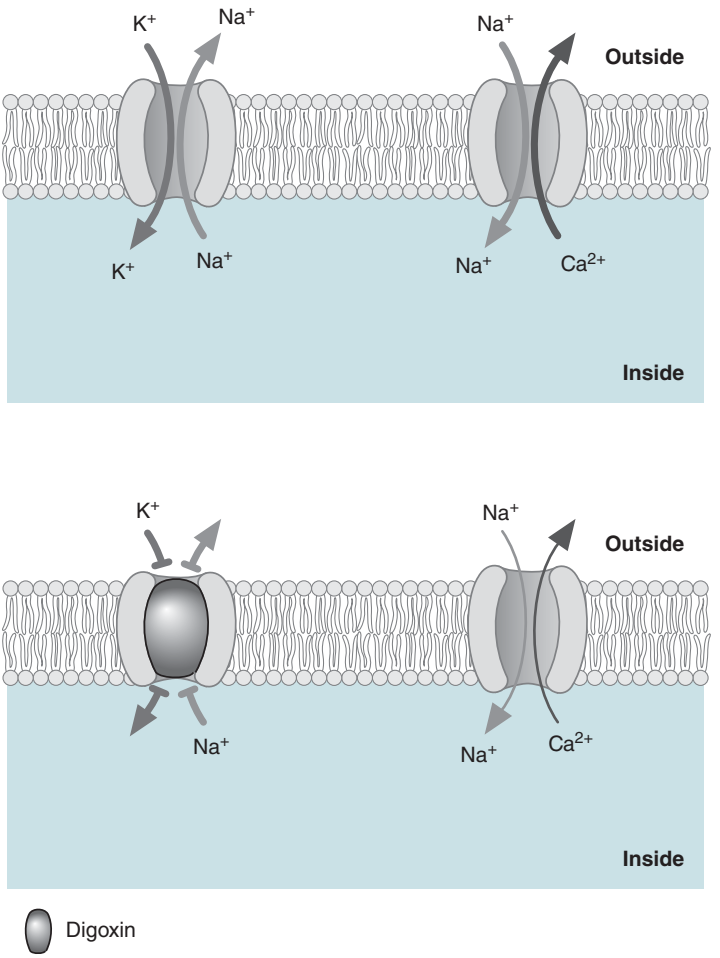

Figure 10–1. Digoxin acts to indirectly increase intracellular calcium levels by binding to the Na^+/K^+-ATPase.

Within the nervous system cardiac glycosides affect both the sympathetic and parasympathetic systems, and parasympatheticomimetic effects predominate at therapeutic doses. **Increased vagal activity inhibits the SA node and delays conduction through the AV node.**

In **acute heart failure, digitalis clearly improves contractility.** EF and cardiac output are increased and symptoms decreased. **In congestive heart failure, digitalis is used primarily in patients who are symptomatic after optimal therapy with diuretics, ACE inhibitors, and beta blockers.** In this setting, digitalis decreases symptoms and increases exercise tolerance. However, in patients with **normal sinus rhythm,** there is **no decline in overall mortality** because of deaths associated with digitalis toxicity.

Because of its action in **increasing vagal tone, cardiac glycosides** are useful in the treatment of **several supraventricular arrhythmias** including **atrial flutter** and

atrial fibrillation. Digitalis can control paroxysmal atrial and AV nodal tachycardia. Its use is **contraindicated in Wolff-Parkinson-White syndrome,** where it can induce arrhythmias in the alternate pathway.

Cardiac glycosides have a **narrow therapeutic index. Toxic levels of cardiac glycosides lead to depletion of intracellular K^+ and accumulation of Na^+** (because of inhibition of Na^+/K^+-ATPase). This leads to partial depolarization of the cell and increased excitability, both of which can lead to arrhythmias, including supraventricular and ventricular tachyarrhythmias. Bradycardia and heart block are also manifestations of digitalis toxicity in the heart. **Adverse effects of digitalis on the gastrointestinal (GI) tract** are common, including **anorexia, vomiting, pain, and diarrhea.** Central nervous system effects include **yellowed and blurred vision, dizziness, fatigue, and delirium.** At very high toxic ranges, digitalis inhibits Na^+/K^+-ATPase in skeletal muscle, resulting in hyperkalemia.

K^+ competes with digitalis for binding to the Na^+/K^+-ATPase and reduces the effectiveness of the drug; **hypokalemia increases the effectiveness of digitalis and increases toxicity.** Hypercalcemia can also increase the action of digitalis and increase toxicity.

Dopamine and dobutamine are positive inotropic agents that can be used on a **short-term basis in congestive heart failure. Dobutamine stimulates D_1- and D_2-adrenergic receptors.** The action on **β_1-adrenoreceptors** is responsible for **most of the beneficial actions of dobutamine.** It is useful in patients with acute left ventricular failure or to prevent pulmonary edema in heart failure. At sufficient doses, **dopamine** interacts with **β_1 receptors** and **increases myocardial contractility.** It is useful in the treatment of **cardiogenic and septic shock**.

Structure

Cardiac glycosides share two structural features: an aglycone steroid nucleus with a lactone at carbon 17 in the D ring, which confers the cardiotonic properties, and polymeric sugar moieties attached to carbon 3 of the A ring. Both features are necessary for pharmacologic activity; the sugar groups are largely responsible for the pharmacokinetic properties of these drugs.

Mechanism of Action

Inhibition of the activity of the Na^+/K^+-ATPase; this indirectly increases intracellular Ca^{2+}.

Administration

Digoxin can be administered IV or orally. Oral bioavailability is approximately 75 percent.

Pharmacokinetics

Digoxin is excreted by the **kidney** and is not metabolized. Patients with compromised renal function must be monitored carefully for digoxin toxicity.

COMPREHENSION QUESTIONS

10.1 Digoxin increases cardiac contractility by directly engaging in which of the following?

A. Activating L-type Ca^{2+} channels
B. Inhibiting cardiac phosphodiesterase
C. Inhibiting myocardial Na^{+}/Ca^{2+}-ATPase
D. Inhibiting myocardial Na^{+}/K^{+}-ATPase

10.2 Which of the following drugs may be used to increase cardiac output in a patient with pulmonary edema secondary to MI?

A. Captopril
B. Dobutamine
C. Metoprolol
D. Verapamil

10.3 Which of the following is the most accurate statement regarding digoxin?

A. Decreases mortality in patients with congestive heart failure with normal sinus rhythm
B. Increases vagal tone and decreases AV node conduction
C. Lengthens the action potential and increases the refractoriness of the heart
D. Useful in the treatment of Wolff-Parkinson-White syndrome

ANSWERS

10.1 **D.** While digoxin reduces the amount of Na^{+}-Ca^{2+} exchange, this effect is indirect and mediated by the inhibition of the Na^{+}/K^{+}-ATPase.

10.2 **B.** Dobutamine is useful in this setting; the other choices would not increase cardiac output.

10.3 **B.** Cardiac glycosides increase vagal tone and decrease AV node conduction. The action potential is decreased and the refractoriness of the heart is decreased. Mortality is not decreased in patients with normal sinus rhythm because of digoxin toxicity. Digoxin is contraindicated in Wolff-Parkinson-White syndrome.

PHARMACOLOGY PEARLS

- Cardiac glycosides inhibit the activity the Na^+/K^+-ATPase; this indirectly increases intracellular Ca^{2+}.
- While several studies have found that digitalis does not improve mortality, it is still useful in reducing symptoms in congestive heart failure.
- The increased effectiveness of digitalis as serum K^+ falls is significant because most patients with congestive heart failure are also frequently treated with diuretics that cause potassium loss.
- Hypokalemia exacerbates digoxin toxicity.

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CASE 11

A 62-year-old man is being managed in the intensive care unit following a large anterior wall MI. He has been appropriately managed with oxygen, aspirin, nitrates, and β-adrenergic receptor blockers but has developed recurrent episodes of ventricular tachycardia. During these episodes he remains conscious but feels dizzy, and he becomes diaphoretic and hypotensive. He is given an IV bolus of lidocaine and started on an IV lidocaine infusion.

- To what class of antiarrhythmic does lidocaine belong?
- What is lidocaine's mechanism of action?

ANSWERS TO CASE 11:
Antiarrhythmic Drugs

Summary: A 62-year-old man develops symptomatic ventricular tachycardia after an MI. He is begun on IV lidocaine.

- **Class of antiarrhythmic to which lidocaine belongs:** I.b
- **Mechanism of action:** Specific Na^+ channel blocker, reduces the rate of phase 0 depolarization, primarily in damaged tissue.

CLINICAL CORRELATION

Lidocaine is a common treatment for ventricular tachycardia in a patient who is symptomatic and remains conscious. It works by blocking Na^+ channels and is highly selective for damaged tissue. This makes it useful for the treatment of ventricular ectopy associated with an MI. It is administered as an IV bolus followed by a continuous drip infusion. It is metabolized in the liver and undergoes a large first-pass effect. It has many neurological side effects, including agitation, confusion, and tremors, and can precipitate seizures.

APPROACH TO:
Pharmacology of the Antiarrhythmics

OBJECTIVES

1. Know the classes of antiarrhythmic agents and their mechanisms of action.
2. Know the indications for the use of antiarrhythmic agents.
3. Know the adverse effects and toxicities of the antiarrhythmic agents.

DEFINITIONS

Paroxysmal atrial tachycardias (PAT): Arrhythmia caused by reentry through the AV node.

Heart block: Failure of normal conduction from atria to ventricles.

WPW: Wolff-Parkinson-White syndrome.

DISCUSSION

Class

Arrhythmias arise as a result of improper impulse generation or improper impulse conduction. The abnormal action potentials cause disturbances in the rate of contraction or in the coordination of myocardial contraction. The molecular targets of

antiarrhythmics are ion channels in the myocardium or conduction pathways; these may be direct or indirect effects.

There are four ion channels of the most pharmacologic importance in the heart:

Voltage-activated Na^+ channel—SCN5A

Voltage-activated Ca^{2+} channel—L-type

Voltage-activated K^+ channel—IKr

Voltage-activated K^+ channel—IKs

Most antiarrhythmic drugs either bind directly to sites within the pore of a channel or indirectly alter channel activity. There are approximately 20 antiarrhythmics approved for use today. They are classified according to which of the ion channels they affect and their mechanism of action (Table 11–1).

The major arrhythmias of clinical concern are ventricular arrhythmias, atrial arrhythmias, bradycardias, and heart blocks. There is also the pharmacologic need to convert an abnormal rhythm to normal sinus rhythm (cardioconversion). The class of antiarrhythmics used for any particular arrhythmia depends on the clinical circumstances. The treatment of acute, life-threatening disease, in contrast with the long-term management of chronic disease, requires a different selection of antiarrhythmics.

Table 11–1 • SELECTED ANTIARRHYTHMIC AGENTS

Class	Prototype Drug	Na^+	K^+	Ca^{2+}	Effect
Ia	Quinidine	X	X		Increases refractory period, slows conduction
Ib	Lidocaine	X			Shortens duration of refractory period and action potential
Ic	Flecainide	X	X		Slows conduction
II	Propranolol			X*	Blocks β_1-adrenergic receptors
III	Amiodarone	X		X	Increases refractory period
IV	Verapamil			X	Increases refractory period AV node
Other	Adenosine		X	X*	Decreases AV node conduction
	Moricizine	X†			Decreases excitability, conduction velocity, automaticity
	Atropine				Decreases vagal tone
	Digoxin				Increases vagal tone
	Sotalol		X‡		Also nonselective beta blocker

*Indirect effect mediated by decreasing cAMP.

†Moricizine blocks Na^+ channels and is usually considered a class 1 antiarrhythmic, but it has properties of Ia, Ib, and Ic drugs.

‡Sotalol has α- and β-adrenergic antagonist properties and also inhibits K^+ channels.

Class I Antiarrhythmics

Class I antiarrhythmics bind to Na^+ channels and prevent their activation. This increases their effective refractory period and decreases conduction velocity. Class I antiarrhythmics have a greater effect on damaged tissue compared to normal tissue. This may be because of several factors:

Depolarization. Damaged tissues tend to be depolarized because of K^+ leakage—many class I antiarrhythmics preferentially bind to depolarized tissues.

pH. Ischemic tissues are more acidic, and many class I antiarrhythmics preferentially bind to membranes at low pH.

Inactivation frequency. During arrhythmias, Na^+ channels undergo more rapid cycles of activation/inactivation. At any given time, there will be an increase in the number of inactive channels compared to normal tissues in a normal rhythm. Class I antiarrhythmics generally bind preferentially to Na^+ channels in the inactive state.

The subclasses a, b, and c of class I antiarrhythmics are distinguished based on their ability to inhibit K^+ channels.

Class Ia. Procainamide is a prototype class Ia antiarrhythmic that suppresses the activity of Na^+ and also suppresses K^+-channel activity. **Administered IV**, it is used for the acute suppression of supraventricular and ventricular arrhythmias and for suppressing episodes of atrial flutter and atrial fibrillation. **It may be administered orally for the long-term suppression of both supraventricular and ventricular arrhythmia, but toxicity limits this application. Procainamide can suppress sinoatrial (SA) and AV nodal activity, especially in patients with nodal disease, and cause heart block. Prolonged use of procainamide is associated with increased risk of ventricular tachycardias. Procainamide has some ganglionic blocking activity and can cause hypotension and decreased myocardial contractility.** A limiting adverse effect of procainamide is the development of lupus-like syndrome characterized by skin rash, arthritis, and serositis. **All patients on procainamide will develop antinuclear antibodies within 2 years.** Procainamide is metabolized to *N*-acetyl procainamide (NAPA), **which has K^+-channel-blocking effects. NAPA is excreted by the kidney, and plasma levels of procainamide and** NAPA should both be monitored especially in patients with renal disease.

Class Ib. Lidocaine is very specific for the Na^+ channel and it blocks both activated and inactivated states of the channel. **It must be administered parenterally. Lidocaine has been used extensively to suppress ventricular arrhythmias associated with acute MI or cardiac damage (surgery). It has been used prophylactically to prevent arrhythmias in patients with MI, but there is controversy as to the overall benefit in decreasing mortality. Lidocaine is metabolized in the liver and has relatively short half-life (60 minutes). This limits its adverse effects, which generally are mild and rapidly reversible.** Overdose can produce sedation, hallucinations, and convulsions. **Mexiletine** is an orally active congener of lidocaine with similar antiarrhythmic properties.

Class Ic. Flecainide inhibits both Na^+ and K^+ channels but shows no preference for inactivated Na^+ channels. It delays conduction and increases refractoriness. **It is effective for the control of atrial arrhythmias and it is very effective in suppressing supraventricular arrhythmias.** A large clinical trial with patients with **ischemic heart disease** demonstrated that flecainide is **associated with increased mortality. Currently its use is restricted to patients with atrial arrhythmias without underlying ischemic heart disease.**

Class II Agents

Endogenous catecholamines increase myocardial excitability and can trigger ventricular arrhythmias. β-Adrenergic receptor blockade indirectly suppresses L-type Ca^{2+}-channel activity. This slows phase 3 repolarization and lengthens the refractory period. Reduction in sympathetic tone depresses automaticity, decreases AV conduction, and decreases heart rate and contractility. **Beta blockers are useful for the long-term suppression of ventricular arrhythmias particularly in patients at risk for sudden cardiac arrest.** Beta blockers are most effective in patients with increased adrenergic activity:

- Surgical or anesthetic stress.
- Anginal pain and MI.
- Congestive heart failure and ischemic heart disease.
- Hyperthyroidism.
- Beta blockers have been shown to reduce mortality and second cardiovascular events by 25–40 percent in patients with post-MI.

There are a large number of beta blockers approved for use as antiarrhythmics. Two of particular interest are the following:

1. **d,l-sotalol,** which is particularly effective as an antiarrhythmic agent because it combines inhibition of K^+ channels with beta-blocker activity
2. Metoprolol, a specific β_1 antagonist, which reduces the risk of pulmonary complications

d,l-sotalol is a racemic mixture; l-sotalol is an effective, **nonselective β-adrenergic antagonist;** and d-sotalol is a class III antiarrhythmic that inhibits K^+ channels. It is an oral agent with a long half-life (20 hours) that can maintain therapeutic blood levels with once-a-day dosing. d,l-sotalol is useful for the long-term suppression of ventricular arrhythmias, especially in patients at risk of sudden death. It is also used to suppress atrial flutter and fibrillation and paroxysmal atrial tachycardia. It is a valuable adjunct in the use of implantable cardiac defibrillators, decreasing the number of events that require defibrillation. At low doses, the β-adrenergic-blocking activity, and associated adverse effects, predominates. At higher doses, the K^+-channel inhibitory effects predominate with the risk of developing ventricular tachycardia.

Class III Antiarrhythmics

Drugs in this class **include bretylium, dofetilide, ibutilide, and amiodarone.** These agents act predominantly to **inhibit cardiac K^+ channels (IKr).** This lengthens the

time to repolarize and prolongs the refractory period. Amiodarone is also a potent inhibitor of Na^+ channels and has α- and β-adrenergic antagonist activity.

Amiodarone has an unusual structure related to thyroxine. It can be administered IV or orally, but its actions differ depending on route of administration. IV-administered amiodarone has acute effects to inhibit K^+-channel activity, slowing repolarization, and increasing the refractory period of all myocardial cell types. Administered orally in a more chronic setting, it leads to long-term alterations in membrane properties with a reduction in both Na^+- and K^+-channel activity and decrease in adrenergic receptor activity. **Amiodarone is used extensively for ventricular and atrial arrhythmias and has little myocardial depressant activity,** allowing it to be used in patients with diminished cardiac function. Administered IV, amiodarone is effective in treating ventricular tachycardia and to prevent recurrent ventricular tachycardia, and to suppress atrial fibrillation. Oral amiodarone is useful for arrhythmias that have not responded to other drugs (such as adenosine) and for long-term suppression of arrhythmias in patients at risk of sudden cardiac death.

Amiodarone has little myocardial toxicity, does not impair contractility, and rarely induces arrhythmias. **Most of the adverse effects of amiodarone result from its long half-life (13–103 days) and poor solubility.** Amiodarone deposits in the lung and can cause **irreversible pulmonary damage.** Similarly, **amiodarone can be deposited in the cornea causing visual disturbances or in the skin where it can cause a bluish tinge. Amiodarone can cause thyroid dysfunction; both hypothyroidism and thyrotoxicosis.**

Class IV Antiarrhythmics

The class IV antiarrhythmics act by directly blocking the activity of L-type Ca^{2+} channels. Verapamil and **diltiazem** are the major members of this class, and they have a similar pharmacology. **Verapamil blocks both active and inactive Ca^{2+} channels** and has effects that are equipotent in cardiac and peripheral tissues. The **dihydropyridines**, such as **nifedipine**, have **little effect on Ca^{2+}channels in the myocardium, but are effective in blocking Ca^{2+} channels in the vasculature. Verapamil** has marked effects on both **SA and AV nodes** because these tissues are highly dependent on Ca^{2+} currents. AV node conduction and refractory period are prolonged and the SA node is slowed. **Verapamil and diltiazem are useful for reentrant supraventricular tachycardias** and can also be used to reduce the ventricular rate in atrial flutter or fibrillation. The **major adverse effect of verapamil** is related to its **inhibition of myocardial contractility.** It can cause heart block at high doses.

Other Antiarrhythmics

Adenosine is a **very short-acting drug (approximately 10 seconds)** used specifically to **block PAT. Adenosine binds to purinergic A1 receptors.** Activation of these receptors leads to increased potassium conductance and decrease in calcium influx. This results in hyperpolarization and a decrease in Ca^{2+}-dependent action potentials. The effect in the AV node is marked with a decrease in conduction and an increase in nodal refractory period. Effects on the SA node are smaller. Adenosine is nearly 100 percent effective in converting PAT to sinus rhythm. Adenosine must be

given IV, and because of its short half-life, it has few adverse effects. Flushing and chest pain are frequent but typically resolve quickly.

Digoxin (see Case 10) blocks Na^+/K^+-ATPase and indirectly increases intracellular Ca^{2+}. In the myocardium this causes an increase in contractility; in nerve tissue the predominant effect is to increase neurotransmitter release; and the parasympathetic system (vagus) is affected more than the sympathetic system. The increased vagal tone results in increased stimulation of muscarinic acetylcholine receptors that slow conduction in the AV node. **Digoxin is very effective in controlling the ventricular response rate in patients with atrial fibrillation or flutter.** Digoxin can be administered IV to acutely treat atrial arrhythmias or orally for long-term suppression of abnormal atrial rhythms. Digitalis is less effective than adenosine in PAT and **should not be used in** Wolff-Parkinson-White syndrome.

Atropine **is a muscarinic antagonist that can be used in some bradycardias and heart blocks. It can be administered to reverse heart block caused by increased vagal tone such as an MI or digitalis toxicity. Atropine is administered IV, and it exerts its effect within minutes.**

COMPREHENSION QUESTIONS

11.1 A 26-year-old woman complains of the abrupt onset of her chest pounding. She is diagnosed with paroxysmal atrial tachycardia. Which of the following is the most effective agent for converting paroxysmal atrial tachycardia to normal sinus rhythm?

A. Adenosine
B. Atropine
C. Digoxin
D. Lidocaine

11.2 Which of the following best describes a pharmacologic property of amiodarone?

A. α-Adrenergic agonist
B. β-Adrenergic agonist
C. Activation of Ca^{2+} channels
D. Inhibition of K^+ channels

11.3 A 45-year-old man is noted to have dilated cardiomyopathy with atrial fibrillation and a rapid ventricular rate. An agent is used to control the ventricular rate, but the cardiac contractility is also affected, placing him in pulmonary edema. Which of the following agents was most likely used?

A. Amiodarone
B. Digoxin
C. Nifedipine
D. Verapamil

ANSWERS

11.1 **A.** Adenosine is nearly 100 percent effective in converting PAT. Digoxin could be used but is less effective.

11.2 **D.** Amiodarone blocks both Na^+ and K^+ channels and has α- and β-adrenoreceptor **antagonist** activities. The latter would indirectly decrease Ca^{2+}-channel activity.

11.3 **D.** Verapamil is a calcium-channel-blocking agent that slows conduction in the AV node, but it also has a negative inotropic effect on the heart.

PHARMACOLOGY PEARLS

- Amiodarone is typically the first choice in acute ventricular arrhythmias.
- Adenosine is the best choice to convert PAT to sinus rhythm.
- Long-term benefit of using class I antiarrhythmics is uncertain, but mortality is not decreased.
- Beta blockers have been shown to reduce mortality and second cardiovascular events by 25–40 percent in patients post-MI.

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CASE 12

A 50-year-old male with a past medical history of hypertension and a history of palpitations presents for follow-up of his hypertension. He is adherant with a low sodium diet, exercises 150 minutes weekly, and is taking his metoprolol at maximum dose (for the HTN and palpitations). His home blood pressure logs and the clinic reading reveal blood pressures in the range 140–150/90–100. The rest of his vitals including heart rate are normal, as his examination. You decide to add a thiazide diuretic to his existing antihypertensive regimen.

- What is the mechanism of action of metoprolol?
- What is the mechanism of action of thiazide diuretics?
- What electrolyte abnormalities commonly occur with thiazide diuretics?

ANSWERS TO CASE 12:
Antihypertensive Agents

Summary: A 50-year-old man with inadequately controlled hypertension is prescribed a thiazide diuretic.

- **Mechanism of action of metoprolol:** β_1-Selective adrenoreceptor antagonist.
- **Mechanism of action of thiazide diuretics:** Inhibit active reabsorption of NaCl in the distal convoluted tubule by interfering with a specific Na^+/Cl^- cotransporter.
- **Electrolyte abnormalities seen with thiazide diuretics:** Hypokalemia, hyponatremia, hypochloremia.

CLINICAL CORRELATION

Thiazide diuretics are the recommended first-line agents for most people with hypertension. They are frequently used in combination with other classes of antihypertensives. Thiazides inhibit the active reabsorption of Na^+. This causes an increase in the excretion of Na^+, Cl^-, and K^+. They also reduce the excretion of Ca^{2+} by increasing its absorption. The excretion of sodium and water reduces intravascular volume and contributes to their antihypertensive effect. Thiazides are used as single agents primarily in mild to moderate hypertension. They are often added as second agents when other drugs alone cannot control a patient's hypertension. The electrolyte abnormalities caused by thiazides can be clinically important. Hypokalemia occurs frequently, especially when higher doses of thiazides are used. Patients need to be instructed to follow a high potassium diet and frequently require potassium supplementation. Thiazides can also elevate serum uric acid levels, which can precipitate gout in susceptible individuals. Thiazides can also worsen hypertriglyceridemia and increase plasma cholesterol.

APPROACH TO:
Pharmacology of Antihypertensive Agents

OBJECTIVES

1. Know the classes of antihypertensive medications and their mechanisms of action.
2. Know the common side effects of the antihypertensive agents.

DEFINITIONS

Hypertension: Blood pressure continuously elevated to levels greater than 140/90 mm Hg on at least 2 separate measurements. Pressures of 121–139/81–89 mm Hg are considered prehypertensive.

Essential hypertension: Hypertension of unknown etiology makes up approximately 90 percent of hypertensive patients.

DISCUSSION

Class

There are 12 major classes of drugs that are used as oral antihypertensive drugs, and these include drugs that act centrally and those that work in the periphery. Antihypertensive drugs may cause vascular smooth-muscle relaxation, vascular volume reduction, or a decrease in cardiac output. This is accomplished by decreasing Ca^{2+} in vascular smooth muscle cells or by reducing Na^{+} reabsorption on the kidney. Table 12–1 lists these major classes. **Lifestyle modifications include smoking cessation, dietary modification (Dietary Approaches to Stop Hypertension [DASH] diet), weight management, and commencement of an exercise program.**

Table 12–1 • SELECTIVE CLASSES OF ANTIHYPERTENSIVE AGENTS

Class	Prototype Drug	MOA	Common Adverse Effect
Beta blocker	Propranolol	Adrenergic	Fatigue, reduction in libido
α_1-Antagonist	Prazosin	Adrenergic receptor antagonist	Orthostatic hypotension
ACE inhibitor	Enalapril	Reduces production of angiotensin II	Hyperkalemia
ARB (angiotensin receptor blocker)	Losartan	AT-1 receptor antagonist	Hyperkalemia
Renin inhibitor	Aliskiren	Inhibits renin activity	Angioedema, headache, dizziness, gastrointestinal events
Specific aldosterone-receptor antagonist	Eplerenone	Aldosterone-receptor antagonists	Hyperkalemia
Diuretic—loop	Furosemide	Reduces Na^{+} reabsorption in loop of Henle	Hypokalemia
Diuretic—distal tubule	Hydrochlorothiazide	Reduces Na^{+} reabsorption at site 3	Hypokalemia
Ca^{2+} channel blocker	Nifedipine	Blocks Ca^{2+} entry in vascular smooth muscle cells	Hypotension arrhythmias
Arterial vasodilators	Minoxidil	HIF1 activation	Orthostatic hypotension
Central acting vasodilator	Clonidine	α_2-Adrenergic agonist	Sedation, depression
Adrenergic neuron blockers	Guanethidine	Inhibits release of norepinephrine	Postural hypotension
Neuronal uptake inhibitor	Reserpine	Depletes neurons of neurotransmitters	Sedation

Table 12–2 • THE JOINT NATIONAL COMMITTEE ON HYPERTENSION HAS DEFINED FOUR CATEGORIES OF HYPERTENSION

Stage	Blood Pressure Systolic (mm Hg)	Blood Pressure Diastolic (mm Hg)	Recommended Treatment
Normal	<120	and <80 or	—
Prehypertensive	121–139	81–89	Lifestyle modification
Hypertensive stage 1	140–159	or 90–99	Lifestyle modification, R_x
Hypertensive stage 2	≥160	or ≥100	Lifestyle modification, R_x

The Joint National Commission (JNC) also emphasized the need to recognize and treat **systolic hypertension,** which is associated with a **higher degree of risk of MI** in patients **older than 45 years.** Systolic hypertension is more difficult to treat than diastolic hypertension and frequently requires multiple drugs acting via different mechanisms.

The JNC-7 report and other recent studies recommend thiazide diuretics as the first-line agent for the treatment of hypertension in most cases **(Table 12–2).** This conservative approach is based on data supporting the fact that these **agents decrease morbidity and mortality** in clinical trials. The other agents that should be considered for initial **monotherapy** include the beta blockers, the renin-angiotensin system inhibitors (either ACE inhibitors or ARBs), α_1-adrenoreceptor antagonists, calcium-channel antagonists, and arterial vasodilators. All have been shown to reduce blood pressure by 10 to 15 mm Hg.

Diuretics

Diuretics cause an initial reduction in blood pressure by **facilitating loss of Na^+ and water.** This leads to a decrease in cardiac output and blood pressure. However, after 8 weeks, cardiac output returns to normal while blood pressure remains reduced. This is thought to be caused by a **reduction in the vasoconstrictive activities of Na^+ on vascular smooth muscles** that include **elevation of intracellular Ca^{2+} via the Ca^{2+}/Na^+ antiporter. Thiazide** diuretics, which reduce the activity of a specific Na^+/Cl^- cotransporter (NCC2) in the **distal convoluted tubule,** are the class of diuretics most often used for hypertension. In refractory cases or in patients with concomitant edema, loop diuretics can be used with caution. Loop diuretics reduce Na^+ reabsorption in the ascending limb of the loop of Henle by reducing the activity of another Na^+-K^+-$2Cl^-$ cotransporter (NKCC) and can produce a profound loss of Na^+ and K^+. **Both thiazides and loop diuretics can cause hypokalemia and hyponatremia.** A common complaint associated with diuretic use is the increased **frequency of urination. Spironolactone and eplerenone are antagonists of the aldosterone receptor and are weakly diuretic. Eplerenone is much more specific for the aldosterone receptor compared to spironolactone.**

Beta (β-) Blockers

Use of β-adrenoreceptor blockers for hypertension relies on **decreasing cardiac output and decreasing peripheral vascular resistance.** The various drugs in this

class vary in their potency on β_1 receptors; **metoprolol** is more than 1000 times more potent in blocking β_1 compared to β_2 receptors, giving this drug a relative **cardioselectivity.** Blockade of β_1-adrenoreceptors in the JGA of the kidney reduces renin secretion, and this reduces the production of angiotensin II. Nonselective beta blockers such as propranolol cause a number of predictable adverse effects including bronchoconstriction (contraindicating use in asthmatics); a decrease in the production of insulin (contraindicating use in diabetics); and central nervous system (CNS) effects including depression, insomnia, and a decline in male potency. In addition, the nonselective agents increase both triglycerides and low-density lipoprotein (LDL). These effects are reduced but not eliminated with the more β_1-selective agents.

Alpha-1 (α_1-) Blockers

Prazosin, doxazosin, and terazosin reduce blood pressure by **antagonizing α_1-adrenoreceptors in vascular smooth muscle.** Blockade of this receptor reduces intracellular **cyclic adenosine monophosphate** (cAMP) and leads to a reduction in intracellular Ca^{2+}. **Orthostatic hypotension** is common on initiation of therapy but diminishes. Dizziness and headache are also adverse effects. α_1-Blockers appear to reduce LDL cholesterol. **Alpha blockers** are used primarily for hypertension in patients who also have symptomatic **prostatic hyperplasia**. Because of excess cases of **congestive heart failure** in users of alpha blockers, these agents should not be used as first-line therapy in hypertension.

Calcium-Channel Blockers

Calcium-channel (Ca^{2+}-channel) blockers are useful antihypertensives and can reduce blood pressure by 10–15 mm Hg. These agents exert their antihypertensive effect by **blocking L-type (voltage-sensitive) Ca^{2+} channels.** By blocking the entry of Ca^{2+} into the cell, less is available to activate the contractile apparatus, and within vascular smooth muscle, this produces a reduction in vascular tone. Three distinct chemical classes comprise the Ca^{2+}-channel antagonists: **dihydropyridines** include nifedipine, diphenylalkylamines include verapamil, and **benzothiazepines** include diltiazem. All are approved for treating hypertension. Nifedipine and the other dihydropyridines have less effect on the heart than verapamil and diltiazem. **Verapamil has the greatest effect on the heart and can significantly reduce contractility.** Because of its effect on the heart rhythm, verapamil can be used to treat supraventricular arrhythmias as well as variant angina. Depression of cardiac function is the greatest adverse effect of the Ca^{2+}-channel blockers, and this is markedly diminished with the dihydropyridines. Dihydropyridines can induce a reflex tachycardia in response to their blood pressure–lowering effect. However, clinical trials with short-acting nifedipine suggested that there was an increase in the risk of MI in patients treated for hypertension, and these agents should not be used to treat the disease.

Renin-Angiotensin System Inhibitors

Inhibitors of the renin-angiotensin system, both **ACE inhibitors, ARBs, and direct renin inhibitors** are effective for hypertension monotherapy. ACE inhibitors block the conversion of the inactive angiotensin I to the potent angiotensin II. Angiotensin II acts to increase blood pressure in several ways. In vascular smooth

muscle, it increases intracellular Ca^{2+} and produces pronounced vasoconstriction. At peripheral nerve endings and in the adrenal medulla, it increases the amount of catecholamines released on stimulation. In the zona glomerulosa of the adrenal cortex, it acts to stimulate the biosynthesis of aldosterone, which increases renal Na^{+} and water retention. Adverse effects include hypotension, dizziness, and fatigue; rarely, hyperkalemia may occur. A dry cough and angioedema may occur as a result of the reduction in degradation of bradykinin that is brought about by these drugs.

Angiotensin II acts through AT-1 and AT-2 receptors, which in turn couple to numerous signal transduction pathways. The hypertensive actions of angiotensin II are mediated by AT-1 receptors. Losartan, valsartan, and other AT-1 receptor blockers are also effective in reducing blood pressure by 10–15 mm Hg. The adverse-effect profile is similar to the ACE inhibitors but without the cough or angioedema.

Aliskiren (Tekturna) reduces the activity of renin; this in turn causes a reduction in the production of angiotensin II. It is about as effective as ACE inhibitors and has fewer side effects and may have greater renoprotective action than ACE inhibitors or ARBs. During clinical trials, headache, dizziness, and some gastrointestinal events were the most common side effects, and angioedema was observed in a few patients.

Direct Arterial Vasodilators

The molecular target of arterial vasodilators is unclear, but all act to decrease intracellular calcium and thereby reduce vascular tone. Minoxidil and hydralazine are the two most commonly used oral vasodilators used to treat hypertension. Hydralazine is thought to act by increasing the activity of the transcription factor HIF-1 (hypoxia inducible factor 1), which regulates a number of downstream genes. Minoxidil may increase the production of nitric oxide and also increases potassium efflux leading to hyperpolarization and a reduction in L-type Ca^{2+} channel activity. Both drugs have pronounced effects on the resistance vessels and little effect on veins. Because of their predominant effect on arterioles, these agents provoke the **baroreceptor reflex that includes tachycardia, vasoconstriction, and the release of renin.** For this reason, these agents are usually combined with a beta blocker and a diuretic.

Centrally Acting Agents

Centrally acting vasodilators such as clonidine and methyldopa act as **α_2-adrenergic receptor agonists in the vasomotor center within the medulla.** These agents decrease sympathetic outflow and thereby decrease vascular tone and cardiac output. The use of these agents as antihypertensives has been overshadowed by the introduction of ACE inhibitors and ARBs and Ca^{2+}-channel blockers. This is largely because of the adverse effects, which are mostly in the CNS and include sedation, depression, and dry mouth. However, they are still used in cases of refractory hypertension.

Peripheral Sympathetic Inhibitors

Peripheral sympatholytic agents used for hypertension include guanethidine and reserpine. Guanethidine enters sympathetic nerve terminals by transport and replaces norepinephrine in transmitter vesicles. Release of norepinephrine is thereby

diminished. Reserpine blocks the uptake and storage of biogenic amines, and this diminishes the amount of transmitter released on stimulation. Because of much higher rates of adverse effects, these agents are rarely used to treat simple hypertension but may be combined in the treatment of refractory hypertension.

COMPREHENSION QUESTIONS

12.1 A 45-year-old man has hypertension. A thiazide diuretic agent had been prescribed with continued elevated blood pressure. The inclusion of spironolactone to the thiazide diuretic is done to achieve which of the following?

A. Reduce hyperuricemia
B. Reduce Mg^+ loss
C. Decrease the loss of Na^+
D. Reduce K^+ loss

12.2 A 42-year-old woman is noted to have Type II diabetes for 20 years. She is noted to have hypertension with BP in the 150/94 range. The urinalysis shows mild proteinuria. Which of the following drugs would be the best to treat the hypertension in this individual?

A. Enalapril
B. Propranolol
C. Hydrochlorothiazide
D. Nifedipine

12.3 A 33-year-old man is diagnosed with essential hypertension. He is started on a blood pressure medication, and after 6 weeks, he notes fatigue, rash over his face, joint aches, and effusions. A serum antinuclear antibody (ANA) test is positive. Which of the following is the most likely agent?

A. Hydralazine
B. Propranolol
C. Thiazide diuretic
D. Nifedipine
E. Enalapril

12.4 68-year-old male with hypertension presents for annual examination. On review of systems he reports urinary hesitancy and nocturia. Your examination reveals a nontender but enlarged prostate without nodules. On review of his blood pressure logs and clinic readings he is averaging values of 150/80 mm Hg. Which of the following medications would offer treatment of the hypertension and prostatic symptoms?

A. Furosemide
B. Aliskiren
C. Propranolol
D. Terazosin

ANSWERS

12.1 **D.** Spironolactone is a "potassium-sparing" diuretic that reduces K^+ excretion in the collecting duct. It diminishes the K^+-wasting effects of thiazide diuretics.

12.2 **A.** ACE inhibitors, such as enalapril, have been shown to reduce the progressive loss of renal function that is often seen in diabetic patients. The nonselective beta blocker, propranolol, would worsen the diabetes.

12.3 **A.** Hydralazine is associated with a lupus-like presentation, with photosensitivity, malar rash, joint pain, and sometimes pericardial effusion or pleural effusion.

12.4 **D.** Terazosin is an α_1-adrenoreceptor antagonist that is a useful antihypertensive. It also reduces symptoms associated with benign prostatic hyperplasia. Patient should be cautioned on side effects of orthostatic hypotension. The goal is to start low and go slow with the dosing to minimize side effects. Furosemide, a loop diuretic, would improve the blood pressure but worsen the nocturia.

PHARMACOLOGY PEARLS

- The ALLHAT clinical trial (antihypertensive and lipid-lowering treatment to prevent heart attack) compared amlodipine, a dihydropyridine Ca^{2+}-channel blocker, lisinopril, an ACE inhibitor, and doxazosin, an α_1-adrenergic antagonist, with chlorthalidone, a thiazide diuretic.
- Thiazide diuretics are the preferred initial therapy for hypertension in most cases.
- Beta-blocking agents can cause depression, insomnia, male impotency, bronchoconstriction, and decreased production of insulin.

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CASE 13

A 60-year-old man with hypertension and type II diabetes comes in for a follow-up visit. Along with making appropriate diet and lifestyle changes, he is taking an ACE inhibitor-thiazide diuretic combination for his hypertension and metformin for his diabetes. His blood pressure and diabetes are under acceptable control. Routine blood work revealed normal electrolytes, renal function, and liver enzymes. He is noted to have elevated total cholesterol and low-density lipoprotein (LDL) levels, which have remained high in spite of his lifestyle changes. In an effort to reduce his risk of developing coronary artery disease, you start him on a 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitor.

- What is the mechanism of action of HMG-CoA reductase inhibitors?
- What effect do they have on total and LDL cholesterol levels?
- What are the common adverse effects of HMG-CoA reductase inhibitors?

ANSWERS TO CASE 13:
Lipid-Lowering Agents

Summary: A 60-year-old man has hypertension, diabetes, and hyperlipidemia and is started on an HMG-CoA reductase inhibitor.

- **Mechanism of action of HMG-CoA reductase inhibitors:** Competitive inhibition of the rate-limiting enzyme in cholesterol biosynthesis results in compensatory increase in plasma cholesterol uptake in the liver mediated by an increase in the number of LDL receptors.
- **Effect on total cholesterol:** Up to 30 percent reduction.
- **Effect on LDL cholesterol:** Up to 50 percent reduction.
- **Common adverse events:** Elevated liver enzymes and hepatotoxicity, myalgia and myositis, irritability, sleep disturbance, anxiety.

CLINICAL CORRELATION

HMG-CoA reductase inhibitors are in wide clinical use with proven benefit in lowering cholesterol levels and reducing the risk of coronary artery disease in susceptible individuals. **They competitively antagonize the rate-limiting enzyme in cholesterol biosynthesis.** Reduced cholesterol synthesis spurs a compensatory increase in hepatic uptake of plasma cholesterol mediated by an increase in the number of LDL receptors. The net effect of this is to lower the plasma levels of lipoproteins, especially LDL cholesterol. The effect on high-density lipoprotein (HDL) cholesterol is less pronounced. Although there are rare cases of severe hepatotoxicity reported with statins, they are generally well tolerated and routine monitoring of liver function studies (LFTs) is no longer required. **Myalgia** is a common side effect, but rarely severe, myositis and rhabdomyolysis have occurred. **Hepatotoxicity and myositis** can occur while using an HMG-CoA reductase inhibitor alone, but they become more likely when combinations of medications are used.

APPROACH TO:
Pharmacology of Lipid-Lowering Drugs

OBJECTIVES

1. Know the drugs used to treat hyperlipoproteinemias.
2. Know the adverse effects and toxicities of the drugs.
3. Know the therapeutic uses of each of the lipid-lowering agents.

DEFINITIONS

Hyperlipidemia: An elevation in either plasma cholesterol or plasma triglycerides or both.

Myopathy: General term for any disease of muscle.

Myositis: Muscle pain with increased creatinine kinase levels.

Rhabdomyolysis: Muscle pain accompanied by a greater than tenfold increase in creatinine kinase above upper limits of normal, indicating serious muscle damage.

LDL cholesterol: Low-density lipoprotein. Atherogenic lipoprotein particle. Several subfractions have been identified, and the smallest are the most atherogenic. It contains apolipoprotein B_{100} (Apo B_{100}; interacts with LDL receptor), Apo E (interacts with LDL receptors and Apo E receptors), and Apo C (activates lipoprotein lipase).

HDL cholesterol: High-density lipoprotein particle involved in transporting cholesterol from the periphery back to the liver. Has antiatherosclerotic activity. Contains Apo A, C, and D.

VLDL: Very-low-density lipoprotein, a triglyceride-rich lipoprotein particle synthesized in the liver.

DISCUSSION

Class

Drugs that decrease plasma lipids are among the most commonly prescribed today. Some of these affect primarily cholesterol (eg, the statins) and are useful in the treatment of hypercholesterolemia while other agents affect primarily triglycerides (eg, gemfibrozil).

The National Cholesterol Education Program (NCEP) has classified levels of plasma cholesterol (Table 13–1). The LDL cholesterol treatment goal is determined

Table 13–1 • NATIONAL CHOLESTEROL EDUCATION PROGRAM (NCEP) LEVELS OF PLASMA CHOLESTEROL

LDL Cholesterol (mg/dL)	Categorization
< 100	Optimal
101–129	Near/above optimal
130–159	Borderline high
160–189	High
> 190	Very high
Total Cholesterol (mg/dL)	
< 200	Desirable
200–239	Borderline high
> 240	High
HDL Cholesterol (mg/dL)	
Men ≥ 40	Protective
Women ≥ 60	Protective

Table 13–2 • RISK FACTORS FOR CARDIOVASCULAR DISEASE
Clinical CVD
Cigarette smoking
Hypertension (BP > 140/90 mm Hg) or on an antihypertensive drug
Low HDL cholesterol (< 40 mg/dL)
Family history of premature coronary heart disease
Age (men > 45 years, women > 55 years)
Poor nutrition

by assessing the risk of cardiovascular disease of individual patients. The major risk factors that modify LDL goals are listed in Table 13–2.

Known coronary heart diseases (CHD) include patients who have had an infarction or angina or a surgical procedure for cardiovascular disease. **In addition, patients with peripheral arterial disease, abdominal aortic aneurism, or symptomatic carotid artery disease or diabetes are considered to have known CHD or a high risk for CHD.** The NCEP classification and the risk assessment are combined and used to modify the LDL cholesterol goals as illustrated in Table 13–3.

AGENTS USED FOR HYPERCHOLESTEROLEMIA

Statins

Of the drugs that decrease plasma cholesterol, the statins have gained the widest use. **The statins are structural analogs of the substrate HMG-CoA that inhibit the activity of the enzyme HMG-CoA reductase** at nanomolar concentrations. This enzyme is required for the synthesis of isoprenoids and cholesterol. By inhibiting de novo biosynthesis of cholesterol, cellular uptake of cholesterol from plasma via the LDL receptor is increased, reducing plasma cholesterol levels. Because **statins have additional actions to inhibit the production of the triglyceride-rich VLDL,** this makes them useful in the management of patients with hypertriglyceridemia; atorvastatin and rosuvastatin are particularly effective in this regard. There is evidence that statins also have anti-inflammatory activity, and this may contribute to their reduction in cardiovascular events. **Statins may also reduce the rate of bone resorption and thereby lessen osteoporosis.** This effect is thought to be caused by the inhibition of isoprenoid biosynthesis in osteoclast precursors, which inhibits their differentiation into mature osteoclasts. A growing body of evidence suggests that statins decrease the risk of stroke, especially in the elderly. Six statins are

Table 13–3 • CARDIOVASCULAR RISK AND LDL GOAL	
LDL Goal	**Risk Level (mg/dL)**
Known CHD	<100
>2 risk factors	<130
0–1 risk factors	<160

approved in the United States: **lovastatin, rosuvastatin, fluvastatin, atorvastatin, pravastatin, and simvastatin.** They differ in efficacy: rosuvastatin has been reported to reduce LDL cholesterol by more than 60 percent; atorvastatin and simvastatin, approximately 50 percent; and pravastatin and fluvastatin, approximately 35 percent. Statins typically increase protective HDL-C, with pravastatin, simvastatin, and atorvastatin reported to cause an 8–10 percent increase. All of the statins are active orally. Lovastatin and simvastatin are prodrugs that are converted to their active metabolite by the liver. Lovastatin, simvastatin, and fluvastatin have relatively short half-lives (1–5 hours) and are most effective if taken at bedtime since the circadian peak of cholesterol synthesis is at night. Rosuvastatin, pravastatin, and atorvastatin have longer half-lives (14–22 hours) and their actions are independent of the time of administration.

The two major adverse effects associated with statin use are hepatotoxicity and myopathy. Hepatotoxicity was initially thought to be as high as 1 percent with elevations in hepatic transaminases as high as 3 times the upper limits. Subsequent clinical trials indicate that the actual incidence of hepatotoxicity is much lower. Muscle pain may occur in as high as 10 percent of patients and is dose dependent. Severe rhabdomyolysis has occurred rarely; however, one statin, cerivastatin, was removed from the market after several rhabdomyolysis-associated deaths.

Bile-Acid-Binding Resins

The bile acid sequestrants are also useful in reducing plasma cholesterol. **Cholestyramine**, colestipol, and colesevelam are ion-exchange resins that nonspecifically bind bile acids within the intestine and thereby reduce their enterohepatic circulation. This increases de novo hepatic bile acid synthesis and the cholesterol for this synthesis comes, in part, from the plasma via the LDL receptor. **Bile acid sequestrants typically reduce plasma cholesterol by 15–20 percent with no effect on triglycerides**. Because they are not absorbed, the bile acid sequestrants are quite safe, and adverse effects are typically gastrointestinal and include bloating and constipation. In the intestine, these agents bind many molecules other than bile acids and they **impair the absorption of lipid-soluble vitamins and many drugs including digoxin, furosemide, thiazides, coumarin, and some statins**. Patient adherence with these drugs is poor.

Inhibitors of Cholesterol Absorption

Ezetimibe is a **different class of cholesterol-lowering drug** that acts **within the intestine to reduce cholesterol absorption.** Cholesterol is absorbed from the small intestine by a process that includes specific transporters that include the Niemann-Pick C1-Like 1 (NPC1L1) protein, which is important for sterol absorption in the gut. Ezetimibe binds to and inhibits the function of NPC1L1, **thereby reducing cholesterol absorption.** Ezetimibe used alone produces a reduction in plasma cholesterol of approximately 19 percent and an approximate 10 percent decline in triglyceride levels. When combined with a statin, reductions in plasma cholesterol as high as 72 percent have been reported in clinical trials. The combination of ezetimibe and low-dose statin can be as effective in lowering LDL-C as maximal doses of a statin—with fewer adverse effects. The complementary mechanisms—inhibition

of cholesterol biosynthesis by statins and inhibition of cholesterol absorption by ezetimibe—may be useful in treating patients with refractory hypercholesterolemia. Few adverse effects have been reported with ezetimibe. The most frequently reported adverse effects are diarrhea (4.1%), arthralgia (3.0%), sinusitis (2.8%), and pain in extremity (2.7%).

Nicotinic Acid

Niacin, at doses well beyond those used as a vitamin, has effects on all plasma lipids. It reduces LDL cholesterol by 20 to 30 percent and reduces **triglycerides** by 35–45 percent. It is the best agent available for **increasing** HDL. Niacin inhibits VLDL production in the liver by inhibiting both the synthesis and esterification of fatty acids. LDL levels are reduced as a consequence of the decline in VLDL synthesis. Niacin inhibits lipolysis in adipose tissue, which reduces the supply of fatty acids to the liver, further decreasing VLDL synthesis. HDL levels are increased because niacin decreases the catabolism of Apo A_1. Niacin is useful in treating hypertriglyceridemia as well as hypercholesterolemia especially in the presence of low HDL. The limiting adverse effect of niacin is **cutaneous flushing and itching, and dyspepsia** is common at the doses (1 g/day) necessary to affect lipids. These adverse effects can be diminished by taking an aspirin 45 minutes prior the niacin. More medically serious adverse effects include hepatotoxicity and hyperglycemia. Niacin can induce an **insulin-resistant state** causing **hyperglycemia**. For this reason, niacin should not be used in diabetic patients.

Agents Used for Hypertriglyceridemia—Fibrates

The fibrates include clofibrate, fenofibrate, ciprofibrate, bezafibrate, and gemfibrozil. These agents predominantly cause a reduction of plasma **triglycerides** and a small decrease in LDL cholesterol. HDL levels are increased. The fibrates bind to a nuclear receptor peroxisomal proliferator-activator receptor γ (PPAR-γ) mostly in liver and skeletal muscle. Agonist-bound PPAR-γ induces lipoprotein lipase (LPL), which increases the lipolysis of triglyceride-rich VLDL and chylomicrons. Fibrates reduce triglycerides by 35 to 50 percent and LDL cholesterol by 10–20 percent. HDL levels are increased by 10 to 15 percent. All of the fibrates are orally active, but their absorption is decreased by food. The major adverse effect is gastrointestinal upset, cutaneous rash, and itching. Fibrates should not be used in patients with compromised renal function.

COMPREHENSION QUESTIONS

13.1 A 54-year-old man is noted to have hyperlipidemia, and is prescribed lovastatin. Lovastatin reduces plasma cholesterol by which of the following processes?

A. Inhibiting Apo B_{100} biosynthesis
B. Inhibiting cholesterol absorption
C. Inhibiting cholesterol biosynthesis
D. Interfering with bile acid reabsorption

13.2 Which of the following is a usual effect of niacin?

A. Increases HDL
B. Increases LDL
C. Increases total cholesterol
D. Increases triglycerides

13.3 A 33-year-old man has been prescribed medication for hyperlipidemia. He has been noted to have bleeding from his gums and easy bruisability. His prothrombin time is elevated. Which of the following agents is most likely to be involved?

A. Atorvastatin
B. Cholestyramine
C. Gemfibrozil
D. Niacin

ANSWERS

13.1 **C.** The statins are competitive inhibitors of HMG-CoA reductase and thereby inhibit de novo cholesterol biosynthesis.

13.2 **A.** Niacin increases HDL, decreases total and LDL cholesterol, and decreases triglycerides.

13.3 **B.** Cholestyramine interferes with the absorption of lipid-soluble vitamins such as vitamin K, leading to decreased levels of vitamin K-dependent coagulation factors.

PHARMACOLOGY PEARLS

- The HMG-CoA reductase inhibitors, the statins, are the initial choice of drug for the treatment of hypercholesterolemia.
- The statins are structural analogs of the substrate HMG-CoA (3-hydroxy-3-methylglutaryl-coenzyme A) that inhibit the activity of the enzyme HMG-CoA reductase.
- The two major adverse effects associated with statin use are myopathy and hepatotoxicity.
- Bile acid sequestrants impair the absorption of lipid-soluble vitamins and many drugs including digoxin, furosemide, thiazides, coumarin, and some statins.
- The fibrates including clofibrate, fenofibrate, ciprofibrate, bezafibrate, and gemfibrozil predominantly cause a decline in plasma triglycerides.
- **Niacin** has effects on all plasma lipids and has side effects of flushing and itching.

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CASE 14

A 19-year-old man is brought to the physician's office by his very concerned mother. He has been kicked out of the dormitory at college for his "bizarre" behavior. He has accused several fellow students and professors of spying on him for the CIA. He stopped attending his classes and spends all of his time watching TV because the announcers are sending him secret messages on how to save the world. He has stopped bathing and will only change his clothes once a week. In your office you find him to be disheveled, quiet, and unemotional. The only spontaneous statement he makes is when he asks why his mother brought him to the office of "another government spy." His physical examination and blood tests are normal. A drug screen is negative. You diagnose him with acute psychosis likely secondary to schizophrenia, admit him to the psychiatric unit of the hospital, and start him on haloperidol.

- What is the mechanism of therapeutic action of haloperidol?
- What mediates the extrapyramidal side effects (EPSs) of the antipsychotic agents?
- Which autonomic nervous system receptors are antagonized by antipsychotic agents?

ANSWERS TO CASE 14:
Antipsychotic Drugs

Summary: A 19-year-old man with acute psychosis likely from schizophrenia is prescribed haloperidol.

- **Mechanism of therapeutic action of haloperidol:** Antagonist activity at postsynaptic dopamine D_2 receptors in the mesolimbic and mesocortical areas of the brain.
- **Mechanism of EPSs:** Antagonist activity at dopamine receptors in the basal ganglia and other dopamine receptor sites in the central nervous system (CNS).
- **Autonomic nervous system receptors blocked by antipsychotic agents:** α-Adrenoceptors and muscarinic cholinoreceptors.

CLINICAL CORRELATION

Schizophrenia is a chronic thought disorder that often presents in adolescence or early adulthood. It is characterized by the presence of "positive symptoms," which include delusions, hallucinations, and paranoia, and "negative symptoms," which include blunt effect, withdrawal, and apathy. The therapeutic effects of the antipsychotic agents result from their antagonist actions on postsynaptic dopamine D_2 receptors in the mesolimbic and mesocortical areas of the brain, although their benefits may also be related to their antagonist activity at dopamine receptors in other areas of the CNS; additionally, atypical antipsychotic agents have efficacy at serotonin receptors. The dopamine receptor antagonist activity of antipsychotic agents at multiple sites in the CNS, and their antagonist activity at various other receptors in the CNS and throughout the body, contributes to the presence of numerous adverse effects. The presence of so many, and frequently severe, side effects makes patient compliance with long-term antipsychotic therapy an important clinical issue. However, newer, "atypical" agents are now available with greater specificity for the receptors that mediate antipsychotic actions than for the receptors that mediate adverse effects.

APPROACH TO:
Pharmacology of Antipsychotic Drugs

OBJECTIVES

1. List the classes and specific drugs that have antipsychotic activity.
2. Describe the mechanism of therapeutic action of antipsychotic agents.
3. Describe the common side effects of antipsychotic agents and indicate the receptors that mediate them.

DEFINITIONS

Acute dystonia: Sustained painful muscle spasms producing twisting abnormal posture usually occurring shortly after taking an antipsychotic medication.

Akathisia: Characterized by feelings of intense muscle restlessness or strong desire to move about, usually during the first 2 weeks of treatment with an antipsychotic medication.

Parkinson syndrome: Characterized by flat affect, shuffling gait, joint rigidity, and tremor that occurs weeks to months after treatment.

Neuroleptic malignant syndrome: Characterized by the acute onset of hyperthermia, muscle rigidity, tremor, tachycardia, mental status changes, diaphoresis, labile blood pressure, and exposure to a neuroleptic. This syndrome is associated with a significant mortality rate and usually occurs within the first few weeks of therapy.

DISCUSSION

Class

Antipsychotic drugs can be classified according to chemical structure as **phenothiazines, butyrophenones,** and an important group with diverse **atypical structures**. The phenothiazines are further subdivided according to side-chain constituents: **aliphatic, piperidine, and piperazine** (Table 14–1).

Although very similar in their therapeutic efficacy, the "low– (oral-) potency" aliphatic and piperidine phenothiazines have a somewhat different adverse effect profile than the "high-potency" agents that include the piperazine phenothiazines, and also thiothixene, and haloperidol.

The newer, atypical agents have generally unique structures; some studies have suggested that they may have greater therapeutic efficacy with regard to the negative symptoms of schizophrenia. They also have been documented to have superior

Table 14–1 • REPRESENTATIVE ANTIPSYCHOTIC DRUGS (SIDE CHAINS)

Phenothiazines
Chlorpromazine, triflupromazine (aliphatic)
Thioridazine, mesoridazine (piperidine)
Fluphenazine, trifluoperazine (piperazine)
Butyrophenone
Haloperidol
Atypical
Clozapine
Risperidone
Olanzapine
Quetiapine
Aripiprazole
Ziprasidone

adverse effect profiles. Recent clinical trials have called into question the safety of several of the newer agents. In summary, individual patient response to antipsychotic agents varies widely and often dictates drug selection.

Administration of the low-potency antipsychotic agents is more likely to result in **autonomic adverse effects** that include **orthostatic hypotension** caused by **α-adrenoceptor blockade, and dry mouth, urinary retention, and tachycardia resulting from blockade of muscarinic cholinoreceptors.** Their blockade of **histamine H_1 receptors in the CNS** results in **sedation.** The still widely used high-potency agents, for example, **haloperidol,** are more likely to result in adverse neurologic effects. Among these are the EPSs**, acute dystonia, akathisia, and Parkinson syndrome,** which occur relatively early in therapy and are thought to be primarily mediated by blockade of **dopamine D_2 receptors** in the nigrostriatal dopamine pathway of the basal ganglia. A **late-occurring tardive dyskinesia** that is often irreversible and that may be a result of the slow development of dopamine receptor supersensitivity also in the basal ganglia is more or less likely to occur with all antipsychotic agents except clozapine. A **potentially fatal neuroleptic malignant syndrome is another serious adverse effect of antipsychotic agents in sensitive patients (1%).** Also, **hyperprolactinemia** in women may occur as a result of enhanced prolactin release from the posterior pituitary, because of antipsychotic drug blockade (phenothiazines, butyrophenones, risperidone) of dopamine D_2 receptors of the tuberoinfundibular dopaminergic pathway, which may lead to amenorrhea, galactorrhea, gynecomastia, decreased libido, and impotence. Weight gain is also a likely effect of many of these antipsychotic agents.

The **atypical agents** are **less likely** than the conventional agents to result in adverse **EPSs.** Like the conventional agents these can also cause potentially fatal neuroleptic malignant syndrome. Although most atypical agents do not cause hyperprolactinemia, risperodone, specifically, similar to conventional agents, can elevate prolactin. However, **weight gain** (clozapine, olanzapine, quetiapine), hypotension, and **sedation** are not uncommon events. Atypical antipsychotics (except aripiprazole and ziprasidone) can exacerbate diabetes and hyperlipidemia, as well as precipitate the onset of these illnesses. Routine lipid and diabetic screening is advised for patients taking these medications. **Seizures** (2–5%) and **agranulocytosis** (2% risk, 10% fatality) limit the use of **clozapine** to patients unresponsive to other agents. Both conventional and atypical agents may also cause QTc prolongation in the ECG, which predisposes the patient to a potentially fatal arrhythmia (torsades de pointes).

Mechanism of Action

The clinically useful antipsychotic drugs block postsynaptic dopamine **D_2 receptors,** although the degree of blockade among the drugs varies greatly in relation to their action on other neuroreceptors, particularly serotonin 5-hydroxytryptamine 2A ($5\text{-}HT_{2A}$) receptors and certain other dopamine receptor subtypes. Aripiprazole has a unique mechanism of action in that it is a partial D_2 agonist.

Antipsychotic drugs appear to exert their therapeutic effect, at least in part, by **inhibition of dopamine's action in the mesocortical and mesolimbic dopaminergic pathways of the CNS.**

Administration

All antipsychotic agents can be administered by either the oral or the parenteral route or both. Long-acting depot forms of antipsychotics improve patient compliance. The typical antipsychotics, fluphenazine decanoate and haloperidol decanoate, are available as parenteral depot preparations. Risperidone microspheres, olanzapine pamoate, and paliperidone palmitate are atypical depot formulations available.

Pharmacokinetics

Most antipsychotic agents are readily but incompletely absorbed. They are highly lipid soluble and have longer clinical duration of action than would be expected from their plasma half-life, probably as a consequence of their deposition in fat tissue.

Thioridazine, which is metabolized to mesoridazine, is the exception to the rule that hepatic metabolism of the antipsychotic agents results in less active metabolites.

Concurrent use of certain antipsychotic agents with other drugs that also block cholinoreceptors may result in additive peripheral and CNS dysfunction.

COMPREHENSION QUESTIONS

14.1 A 37-year-old man with psychosis has been treated with haloperidol. He has been developing Parkinson-like symptoms. Haloperidol-induced Parkinson syndrome is a result of haloperidol's action in which of the following tracts?

A. Mesocortical tract
B. Mesolimbic tract
C. Nigrostriatal tract
D. Tuberoinfundibular tract

14.2 The therapeutic effect of haloperidol is mediated, at least in part, by its blockade of which of the following receptors?

A. α-Adrenoceptors
B. Dopamine D_2 receptors
C. Histamine H_1 receptors
D. Muscarinic receptors

14.3 Compared to the low-potency phenothiazine antipsychotic agents, haloperidol is more like to cause which of the following adverse effects?

A. Akathisia
B. Orthostatic hypotension
C. Sedation
D. Urinary retention

14.4 A 30-year-old woman is diagnosed with schizophrenia. Treatment is being weighed between typical and conventional antipsychotic agents. An advantage of atypical antipsychotic agents over conventional antipsychotics is:

A. Cheaper cost
B. Less tardive dyskinesia
C. Specificity for antagonism on D_2 receptors
D. Less likely to cause diabetes

14.5 A 59-year-old male with schizophrenia and obesity presents for routine monitoring. He is currently on olanzapine as he developed tardive dyskinesia on haloperidol. This patient should be screening for which of these conditions due to his medication?

A. Hemachromatosis
B. Diabetes
C. Hemolysis
D. Malignancy

ANSWERS

14.1 **C.** Haloperidol-induced Parkinson syndrome is a result of inhibition of dopamine D_2 receptors in the nigrostriatal tract of the CNS.

14.2 **B.** Antipsychotic drugs like haloperidol exert their therapeutic effect, at least in part, by inhibition of dopamine's action at dopamine D_2 receptors in the mesocortical and mesolimbic dopaminergic pathways of the CNS. A number of adverse effects of these drugs are caused by inhibition of dopamine action in the nigrostriatal and tuberoinfundibular dopaminergic pathways of the CNS; blockade of histamine, muscarinic, cholinergic, and α-adrenergic receptors in the CNS and the peripheral nervous system are also contributory.

14.3 **A.** Haloperidol is most likely to cause dystonia, akathisia, and Parkinson syndrome, whereas the low-potency phenothiazines are more likely to cause autonomic adverse effects that include orthostatic hypotension, sedation, and urinary retention.

14.4 **B.** Although tardive dyskinesia can occur with atypical agents, the frequency of this adverse effect is less frequent than with conventional agents. Because most of the atypical agents are still under patent protection, they are more expensive than the older, conventional agents. Atypical antipsychotics have divers actions on neuroreceptors, including antagonism of D_2 receptors and action on serotonin receptors. Exacerbation or new onset of diabetes is more frequent with the atypical antipsychotics, except for aripiprazole and ziprasidone.

14.5 **B.** Atypical antipsychotics such as in this case have reduced motor side effects compared to the typical agents such as haloperidol. However, they have been associated with worsening metabolic parameters with respect to blood sugar and serum lipids.

PHARMACOLOGY PEARLS

- The low-potency antipsychotic agents are more likely to result in autonomic adverse effects that include orthostatic hypotension as a consequence of α-adrenoceptor blockade, dry mouth, urinary retention, and tachycardia resulting from blockade of muscarinic cholinoreceptors, and sedation (histamine H_1-receptor blockade).
- High-potency agents, for example, haloperidol, are more likely to result in EPSs, acute dystonia, akathisia, and Parkinson syndrome, mediated by blockade of dopamine D_2 receptors in the nigrostriatal pathway of the basal ganglia.
- A late-occurring tardive dyskinesia is often irreversible and is a serious effect of many antipsychotic agents.
- A potentially fatal neuroleptic malignant syndrome is another serious adverse effect of antipsychotic agents in sensitive patients.
- Hyperprolactinemia may occur as a result of enhanced prolactin release from the posterior pituitary, as a result of antipsychotic drug blockade of dopamine D_2 receptors in the tuberoinfundibular tract.
- Agranulocytosis may occur in patients treated with clozapine.
- Atypical antipsychotics can cause metabolic syndrome.

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CASE 15

A 30-year-old woman presents to your office for the evaluation of fatigue. For the past 2 months she has felt run down. She says that she doesn't feel like participating in activities that she previously enjoyed, such as her weekly softball games. She has not been sleeping well and has not had much of an appetite. On questioning, she admits to feeling "down in the dumps" most of the time and has found herself crying frequently. She has never gone through anything like this before. She denies any thoughts of wanting to hurt herself or anyone else. She denies any symptoms now or previously of mania. She also denies any visual/auditory hallucinations, paranoia, delusions, or other psychotic symptoms. Other than becoming tearful during her interview, her physical examination is normal. Her blood tests, including a complete blood count and thyroid function, are normal. A serum pregnancy test is negative. You diagnose her as having a major depression and, along with referring her for counseling, start her on fluoxetine.

- What is the mechanism of action of fluoxetine?
- What are the common side effects of fluoxetine?

ANSWERS TO CASE 15:
Antidepressant Agents

Summary: A 30-year-old woman with major depression is prescribed fluoxetine.

- **Mechanism of action of fluoxetine:** Inhibition of the reuptake of serotonin (5-hydroxytryptamine, 5-HT) at the prejunctional nerve terminal.
- **Common side effects:** Headache, nausea, agitation, insomnia, and sexual disturbances (loss of libido and erectile dysfunction).

CLINICAL CORRELATION

Selective serotonin reuptake inhibitors (SSRIs) are the most frequently prescribed antidepressant medications. **They act by inhibiting the reuptake of serotonin by the prejunctional nerve terminal, allowing more serotonin to interact with postjunctional neurons in the central nervous system (CNS).** This is thought to mediate their therapeutic effect. They have been highly effective in the treatment of major depressive disorders and have an excellent safety profile. Unlike tricyclic antidepressants (TCAs), which have multiple severe and potentially fatal effects in an overdose, SSRIs have relatively few severe toxicities and a very low potential for fatality in an overdose. SSRIs do have several side effects of clinical significance. They often cause headache and gastrointestinal (GI) side effects such as nausea. In some cases, agitation, anxiety, and insomnia can be exacerbated. Many of these SSRI side effects tend to be temporary and can often be improved with dose reduction. Another common side effect of SSRIs is **sexual disturbance.** Decreased libido and erectile dysfunction occur frequently and do not generally spontaneously resolve while continuing SSRI therapy, often leading to reduced patient compliance. When diagnosing and treating depression, it is imperative to distinguish between unipolar versus bipolar depression. Agents used for unipolar depression (which major depression fits under) can cause an exacerbation of manic symptoms if used alone for major depression.

APPROACH TO:
Pharmacology of Antidepressant Drugs

OBJECTIVES

1. List the classes of antidepressant agents.
2. Contrast the mechanisms of action of the antidepressant agents.
3. Contrast the adverse effects and toxicities of the antidepressant agents.
4. Describe the indications and contraindications to antidepressant drug use.

DEFINITIONS

Major depressive disorder: Unexplained, long-term difficulty coping with life events characterized by an inability to experience pleasure, abnormal sleep, decreased libido and appetite, feelings of guilt, and suicidal ideation.

DISCUSSION

Class

Drugs used to treat depression are classified as **SSRIs, serotonin and norepinephrine reuptake inhibitors (SNRIs), TCAs and tetracyclics,** and **monoamine oxidase inhibitors (MAOIs).** Other conditions for which certain antidepressant agents are used include panic disorder, obsessive-compulsive disorder (OCD), bipolar affective disorder, chronic pain, and enuresis.

SSRIs are the most extensively prescribed antidepressant agents because, unlike tricyclic agents, they produce **less sedation, have fewer antimuscarinic effects,** and are **safer** in an overdose. Nevertheless, they **may cause sexual disturbances, GI dysfunction, headache, and stimulation (insomnia, tremor, and anxiety).**

TCAs may cause sedation, tremor, insomnia, blurred vision, constipation, urinary hesitancy, weight gain, and sexual disturbances. The MAOIs may cause weight gain, sexual disturbances, and sleep disturbances. **Bupropion is contraindicated in patients with seizure disorders (Table 15–1).**

Drug interactions of TCAs include additive sedative effects with other sedatives, particularly alcohol. **MAOIs,** by increasing catecholamine stores, sensitize patients to indirectly acting sympathomimetic agents, including **tyramine** that is contained in many **fermented foodstuffs (red wine or aged cheese).** Together MAOIs and sympathomimetics agents can result in a severe and sometimes **fatal hypertensive episode. MAOIs and SSRIs can interact to cause a potentially lethal serotonin syndrome** that includes **tremor, hyperthermia, muscle rigidity, and cardiovascular collapse. All antidepressant agents now carry a "black-box warning" of an increased risk of suicidality, especially when used in children and adolescents.**

Structure

TCAs have a three-ring nucleus similar to that of the antipsychotic phenothiazine agents. The MAOIs are subclassified as hydrazides (phenelzine) or nonhydrazides (tranylcypromine).

Mechanism of Action

The therapeutic activity of most of the available therapeutic antidepressant agents is due, at least in part, to their actions on norepinephrine and serotonin.

As the name implies, SSRIs selectively block the prejunctional neuronal uptake transporters in the CNS that terminate serotonin neurotransmission, thus allowing increased activity at serotonin receptors. SNRIs block the reuptake of both serotonin and norepinephrine.

The TCAs also block the prejunctional neuronal uptake transporters in the CNS that terminate norepinephrine and serotonin neurotransmission, thus allowing increased activity at their respective receptors. Amoxapine also blocks dopamine receptors.

The atypical agents have a variety of pharmacodynamic effects. Some act similar to the TCAs, whereas others act as inhibitors at certain subtypes of the serotonin receptor (trazodone, mirtazapine, nefazodone). Mirtazapine also blocks the prejunctional α_2-adrenoceptor to enhance serotonin and norepinephrine neurotransmission.

The MAOIs essentially irreversibly bind to and inhibit the activity of monoamine oxidase (A and B forms). New enzyme must be synthesized to restore activity. As a result of their actions, both drugs prevent prejunctional metabolism of norepinephrine and serotonin, thus allowing more to accumulate and to be released on nerve stimulation.

The neurochemical and biochemical actions described for the antidepressant agents occur soon after their administration. However, the therapeutic effect of these drugs may not be apparent for up to several weeks with continued administration. Thus, considerable attention has been devoted to discovering the long-term neurochemical and biochemical actions of the antidepressant agents that may correlate better with their clinical effectiveness.

The antidepressant agents also produce a myriad of adverse effects that, depending on the agent, may be caused by blockade of histamine receptors, adrenoceptors, and cholinergic receptors in the peripheral and central nervous systems (see Discussion, Class, and Table 15–1).

Administration

Dosing, which may be by the oral or parenteral routes, is determined empirically in relation to the therapeutic response and the patient's tolerance of adverse effects. Selegeline transdermal is the only antidepressant available in a patch formulation.

Pharmacokinetics

Metabolism of the SSRI fluoxetine results in an active metabolite, norfluoxetine, which has a long half-life. Fluoxetine and paroxetine inhibit a number of liver microsomal enzymes, particularly P450 2D6, that can cause clinically significant drug-drug interactions. Nefazodone inhibits cytochrome P450 3A4, which can result in increased levels of other drugs that are dependent on this metabolic pathway for their inactivation.

Monodemethylation by the liver of the tertiary amines TCAs amitriptyline and imipramine results in, respectively, the active metabolites nortriptyline and desipramine. Venlafaxine has an active metabolite, *O*-desmethylvenlafaxine.

Table 15–1 • ANTIDEPRESSANT AGENTS

Antidepressant Agents	Selected Adverse Effects
Selective Serotonin Reuptake Inhibitors Citalopram Escitalopram Fluoxetine Fluvoxamine Paroxetine Sertraline	Sexual dysfunction, GI dysfunction, insomnia, tremor, anxiety
Selective Serotonin and Norepinephrine Reuptake Inhibitors Desvenlafaxine Duloxetine Venlafaxine	Similar to SSRIs, sweating, dizziness, hypertension
Tricyclic Agents Amitriptyline Amoxapine Clomipramine Desipramine Doxepin Imipramine Nortriptyline Protriptyline Trimipramine	Sedation, tremor, blurred vision, constipation, urinary hesitancy, weight gain, and sexual disturbances
Monoamine Oxidase Inhibitors Phenelzine Selegiline transdermal Tranylcypromine	Weight gain, sexual disturbances, sleep disturbances
Atypical Agents Bupropion Maprotiline Mirtazapine Nefazodone Trazodone	*Bupropion:* CNS stimulation, seizures at high doses (up to 0.4%) *Maprotiline:* Like TCAs *Mirtazapine:* Sedation, weight gain *Nefazodone:* Mild sedation, drug-drug interactions, hepatotoxicity *Trazodone:* Sedation, dizziness, orthostatic hypotension, priapism

COMPREHENSION QUESTIONS

15.1 An 18-year-old man is diagnosed with major depression. He also has idiopathic epilepsy. Which of the following agents is contraindicated in this patient?

A. Bupropion

B. Fluoxetine

C. Mirtazapine

D. Venlafaxine

15.2 The antidepressant action of imipramine is thought to be caused by which of the following?

A. Blockade of prejunctional α_2-adrenoceptors

B. Blockade of prejunctional neuronal norepinephrine and serotonin uptake transporters in the CNS

C. Increased numbers of α-adrenoceptors

D. Inhibition of monoamine oxidase

15.3 A 30-year-old man is being treated with isoniazid chemoprophylaxis for an exposure to TB. Which of the following antidepressant agents inhibits hepatic microsomal enzymes to cause clinically significant drug-drug interactions?

A. Fluoxetine

B. Imipramine

C. Phenelzine

D. Trazodone

ANSWERS

15.1 **A.** Bupropion causes seizures in a small but significant number of patients. This number is reduced with use of the slow-release form.

15.2 **B.** Imipramine and other TCAs block prejunctional neuronal norepinephrine and/or serotonin uptake transporters in the CNS. Phenelzine and tranylcypromine inhibit monoamine oxidase. The heterocyclic agent mirtazapine blocks prejunctional α_2-adrenoceptors to enhance serotonin and norepinephrine neurotransmission.

15.3 **A.** The SSRI fluoxetine inhibits cytochrome P450 and therefore can significantly elevate the level of other drugs metabolized by these hepatic enzymes.

PHARMACOLOGY PEARLS

- SSRIs are the most commonly prescribed antidepressants because of their favorable side effect profile. Sexual disturbances and GI effects are common, however.
- TCAs may lead to toxicity as a result of cardiac arrhythmias.
- The antidepressant agents are roughly equivalent in their therapeutic action. However, individual patients may respond to, or tolerate, one better than another.
- Small beginning doses of many antidepressant agents are usually preferred because with time tolerance may occur to some of their adverse effects.
- Bupropion is contraindicated in patients with seizure disorders.

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CASE 16

A 29-year-old man is brought to the emergency center in a drunken stupor. He is accompanied by his wife, who states that he hasn't been himself at all for the past few months. According to his wife, he was evaluated for depression by his personal physician about 3 months ago and started on an SSRI. He responded quite well to this therapy over the subsequent 2 months. He started feeling so good and so energetic that he stopped taking his medication. He found that he needed less and less sleep, to the point where he is now only sleeping 2 to 3 hours a day. He has been showering his wife with very expensive gifts and has hit the maximum limit on all of their credit cards. He has been extremely romantic and more interested in sexual relations than at any time before. He has also started drinking heavily and has passed out drunk more than once. His work has suffered, and his boss said that he was in danger of being fired if things didn't straighten out. Other than being drunk, his physical examination and blood tests are normal. He is admitted to the psychiatric unit with a diagnosis of bipolar disorder and started on lithium.

- What is the mechanism of action of lithium?
- What are the common side effects of lithium?
- What is the mechanism of lithium-induced polyuria?

ANSWERS TO CASE 16:
Lithium

Summary: A 29-year-old man is diagnosed with bipolar disorder and is started on lithium.

- **Mechanism of action of lithium:** Not entirely known but may be related to inhibition of membrane phospholipid turnover with a reduction in key second messengers, important in the overactivity of catecholamines thought to be related to mood swings characteristic of bipolar disorder.
- **Common side effects of lithium:** Nausea, vomiting, diarrhea, tremor, edema, weight gain, polydipsia, and polyuria.
- **Mechanism of lithium-induced polyuria:** Renal collecting tubule becomes resistant to antidiuretic hormone.

CLINICAL CORRELATION

Lithium (Li^+) is an effective treatment for bipolar disorder. It is administered orally as lithium carbonate and eliminated almost entirely through the kidney. **Lithium has a narrow therapeutic window.** Even at therapeutic levels (0.5–1.4 mM/L), there are frequent side effects. These include **GI side effects, tremor, edema, polydipsia, and polyuria,** as well as diabetes insipidus and weight gain. It can cause a **benign thyroid enlargement** and even overt **hypothyroidism** (5%). It has been associated with congenital malformations when used during pregnancy. Frequent monitoring of blood levels is critical. There are potentially serious adverse effects at somewhat higher levels (above 2 mM/L). These include **confusion, dizziness, ataxia, and vomiting. At even higher blood levels (above 2.5 mM)**, symptoms may progress to include **seizures, circulatory collapse, and even coma.** Lithium also has significant drug interactions that may increase its blood levels. Increased sodium clearance or depletion, such as caused by thiazide diuretics, some nonsteroidal anti-inflammatory drugs (NSAIDs; but not aspirin or acetaminophen), or severe vomiting and diarrhea, can lead to the increased renal reabsorption of lithium, thus causing toxicity.

APPROACH TO:
Pharmacology of Lithium

OBJECTIVES

1. Describe the mechanism of action of lithium.
2. List other pharmacologic agents used to treat bipolar disease.

DEFINITIONS

Bipolar affective (manic-depressive) disorder: Bipolar disorder is characterized by decreased need for sleep, elevated or irritable mood, hyperactivity, and increased risk-taking behavior, alternating in a cyclic fashion with symptoms of depression.

Mania: A state of abnormally elevated mood.

Major depressive disorder: Also termed unipolar depression, it is characterized by depressed mood, generalized lack of interest in activities, difficulty with concentration, changes in sleep and weight, feelings of worthlessness, and suicidal ideations.

DISCUSSION

Class

In addition to Li^+, the antiepileptic drugs valproic acid, carbamazepine, and lamotrigine and the atypical antipsychotic agents are first-line drugs for the treatment of bipolar disease. These agents are referred to as mood stabilizers. Their adverse effect profiles when used to treat manic depression are generally milder than for lithium (see Case 18).

Structure

Lithium is a small, monovalent cation that is similar in its properties to sodium and that enters cells through Na^+ channels.

Mechanism of Action

Lithium has a number of actions that may have some relationship to its therapeutic activity, including its effects on the synthesis and release of the neurotransmitters norepinephrine, serotonin, and dopamine. Cation transport in nerve and muscle is affected by lithium. Lithium's best-studied effect is on the phosphoinositide second messenger signaling cascade. It inhibits the key inositol phosphatase enzyme, inositol monophosphatase, with depletion of free inositol that is necessary for the activity of the second messengers inositol triphosphate (IP_3) and diacylglycerol (DAG), which mediate the cellular actions of G-protein-coupled muscarinic cholinoreceptors, α-adrenoreceptors, and serotonin 5-HT_2 receptors.

Administration

Lithium, as lithium carbonate, carbamazepine, and valproic acid are administered orally. In addition, valproic acid can be administered IV.

Pharmacokinetics

Lithium has a relatively slow onset of therapeutic action (valproic acid's effects can be achieved in a few days).

More than 90 percent of Li^+ is excreted into the urine, but only 20 percent is cleared. Lithium is actively reabsorbed in the proximal tubule in competition with and at the same sites as Na^+. Sodium depletion as a result of a low-Na^+ diet, as well as diarrhea or vomiting, concomitant use of diuretics, or even sweating, can lead to increased Li^+ retention and toxicity.

Because the renal clearance of lithium increases during pregnancy and then decreases following delivery, careful monitoring of lithium concentrations is necessary to avoid toxicity.

COMPREHENSION QUESTIONS

16.1 A 22-year-old man is diagnosed with bipolar mood disorder and is started on lithium. The therapeutic action of Li^+ is thought to be caused by direct inhibition of which of the following?

A. Inositol monophosphatase
B. Inositol trisphosphate (IP_3)
C. Diacylglycerol (DAG)
D. Muscarinic cholinoreceptors

16.2 The renal clearance of Li^+ may increase with which of the following?

A. Diarrhea
B. Diuretics
C. NSAIDs
D. Pregnancy

16.3 Which of the following is the most likely adverse effect of Li^+ at therapeutic doses?

A. GI dysfunction
B. Hyperthyroidism
C. Oliguria
D. Thrombocytopenia

ANSWERS

16.1 **A.** The therapeutic action of Li^+ is thought to be caused by direct inhibition of inositol monophosphatase. Its effects on IP_3, DAG, and muscarinic cholinoceptor activities are an indirect consequence of this inhibition.

16.2 **D.** The renal clearance of Li^+ may increase with pregnancy, which may lead to a reduction in its therapeutic effect. Diarrhea, certain NSAIDs, and diuretics that result in hyponatremia decrease the renal clearance of Li^+, which may result in more severe adverse effects.

16.3 **A.** GI dysfunction, polydipsia (and polyuria), and hypothyroidism are adverse effects of Li^+ that may occur at therapeutic doses.

PHARMACOLOGY PEARLS

- Measurement of serum lithium concentrations are used routinely to carefully monitor treatment and to evaluate the likelihood of toxicity.
- Lithium is associated with thyroid enlargement; hypothyroidism; diabetes insipidus; diarrhea, nausea, and vomiting; and weight gain. It has been associated with congenital malformations when used in pregnancy.
- Lithium has a relatively slow onset of therapeutic action, and therefore antipsychotic drugs or benzodiazepines are used acutely to calm seriously agitated patients with bipolar affective disorder.
- Antidepressant agents may precipitate mania and induce more rapid cycling in some patients.

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CASE 17

A 66-year-old man comes in to your office for evaluation of a tremor. He has noticed a progressively worsening tremor in his hands for the past 6 months. The tremor is worse when he is resting and improves a little when he reaches for an object or is using his hands. He has also noticed that it is harder to "get started" when he stands up to walk. He takes several small, "shuffling" steps before he can reach his full stride. He has no significant medical history and takes only an aspirin a day. On examination you note that his face is fairly expressionless; he has a pill-rolling-type tremor of his hands at rest and has cogwheel rigidity of his arms. You diagnose him with Parkinson's disease and prescribe a combination of levodopa (L-dopa) and carbidopa.

- What is the most common cause of the symptoms of idiopathic Parkinson's disease?
- What is the mechanism of action of L-dopa?
- Why is L-dopa usually given in combination with carbidopa?

ANSWERS TO CASE 17:
Drugs Used to Treat Parkinson's Disease

Summary: A 66-year-old man is diagnosed with idiopathic Parkinson's disease and started on L-dopa and carbidopa therapy.

- **Cause of symptoms of idiopathic Parkinson's disease:** Degeneration of dopamine-producing neurons in the substantia nigra.
- **Mechanism of action of L-dopa:** L-dopa is decarboxylated in prejunctional neurons in the central nervous system (CNS) to restore dopamine (DA) activity in the corpus striatum.
- **Reason L-dopa is given with carbidopa:** Carbidopa inhibits peripheral but not central dopa-decarboxylase metabolism of L-dopa. Thus, because a greater fraction enters the CNS, the therapeutic dose can be reduced and certain adverse effects minimized.

CLINICAL CORRELATION

Parkinson's disease is a progressive, degenerative movement disorder. Symptoms of idiopathic Parkinson's disease are caused by the degeneration of dopamine-producing neurons in the substantia nigra. Loss of dopamine causes an imbalance between dopaminergic and cholineregic neurotransmission. Dopamine inhibits the release of gamma (γ)-aminobutyric acid (GABA) from GABAergic neurons in the corpus striatum, whereas acetylcholine stimulates GABA release from these same neurons. Striatal neurons affect motor activity via pathways leading to the thalamus and cerebral cortex and regulate dopamine output by a feedback loop. The overall physiologic effect is to reduce excitation of spinal cord motor neurons. The clinical effect is the classic parkinsonian movement disorder. Symptoms of Parkinson's disease include a resting tremor, bradykinesia, masked facies, loss of postural reflexes, and rigidity.

Replacement of dopamine can help to restore the balance of activity between dopamine and acetylcholine; depletion of acetylcholine is also effective. Dopamine does not cross the blood-brain barrier into the CNS, but L-dopa, a dopamine precursor, can pass into the CNS where it is decarboxylated to dopamine. Dopamine interacts with postsynaptic dopamine D_2 receptors to inhibit GABAergic neuron activity in the striatum. L-dopa, however, is rapidly converted to dopamine in the periphery by a decarboxylase enzyme. If given by itself, high doses of L-dopa would be needed to provide a beneficial clinical effect in the CNS. **For that reason, L-dopa is given in combination with carbidopa,** which itself **does not cross the blood-brain barrier,** and which **inhibits peripheral, but not CNS, dopamine decarboxylase.** This allows therapeutic levels of L-dopa to enter the CNS at lower doses than would otherwise be necessary. The addition of carbidopa to L-dopa decreases the incidence and severity of peripherally mediated adverse effects that would occur with L-dopa alone, such as nausea, vomiting, and orthostatic hypotension.

Nevertheless, even with carbidopa, L-dopa has many clinically important adverse effects. **Involuntary dyskinesias** are observed in up to 90 percent of patients, perhaps

caused by dopamine receptor supersensitivity, and often limit the use of this therapy. The end of dose and on-off akinesias may require reducing the dosing intervals or the use of sustained-release preparations. **Behavioral effects are also common, including depression, insomnia, nightmares, changes in mood, compulsive behaviors, and hallucinations. Nausea, vomiting, anorexia,** and **orthostatic hypotension** are not uncommon.

APPROACH TO:

Pharmacology of Drugs Used to Treat Parkinson's Disease

OBJECTIVES

1. List and explain the mechanisms of action, major adverse effects, and contraindications to the use of L-dopa and carbidopa combination to treat Parkinson's disease.
2. List other drugs or drug classes used to treat Parkinson's disease, and describe their mechanisms of action, benefits, and adverse effects.

DEFINITIONS

Tremor: Rhythmic oscillations of a body part, usually at a joint. In Parkinson's disease tremor is present when there is minimal voluntary activity (tremor at rest).

Dyskinesia: Repetitive involuntary choreiform (dance-like) movements of the limbs, hands, trunk, and tongue.

Akinesia: Decreased voluntary movement.

Bradykinesia: Slow movements.

On-off effect: Sudden onset of parkinsonian symptoms with a usual therapeutic dose of L-dopa that may be the result of progression of the disease with loss of dopamine nerve terminals in the striatum.

DISCUSSION

Class

In addition to L-dopa, there are several other drug classes used to treat Parkinson's disease, including the **dopamine agonists: bromocriptine, pramipexole, and ropinirole; the selective MAOI: selegiline; the catechol-O-methyltransferase (COMT) inhibitors: entacapone and tolcapone; the antiviral drug: amantadine; and muscarinic cholinoreceptor-blocking agents: benztropine, biperiden, orphenadrine, procyclidine, and trihexyphenidyl** (Table 17–1).

Dopamine agonists may be used alone or as an adjunct to L-dopa. Alone, there is a lower incidence of dyskinesia and response fluctuations. With L-dopa/carbidopa, dopamine agonists can be used to compensate for the diminishing effect of L-dopa that occurs after 3 to 5 years of use. This reduced L-dopa efficacy presumably results from progressive destruction of the substantia nigra and loss of dopaminergic

Table 17–1 • SELECTIVE LIST OF PARKINSON AGENTS

Drugs For Parkinson's Disease	Adverse Effects
L-dopa	Dyskinesias, depression, insomnia, nightmares, changes in mood, nausea, vomiting, anorexia, orthostatic hypotension
Dopamine Agonists Bromocriptine Pramipexole Ropinirole	Like L-dopa
MAOI	
Selegiline Rasagiline	Insomnia, serotonin syndrome (with meperidine, SSRIs, TCAs)
COMT Inhibitors Entacapone Tolcapone (tolcapone)	GI disturbances, dyskinesias, sleep disturbances, orange discoloration of the urine, hepatotoxicity
Amantadine	Restlessness, insomnia, hallucinations, depression, livedo reticularis
Muscarinic cholinoreceptor blockers Benztropine Biperiden Orphenadrine Procyclidine Trihexyphenidyl	Dry mouth, blurred vision, mydriasis, urinary retention, drowsiness, confusion, hallucinations

neurons. Adverse effects, which are less severe with pramipexole and ropinirole, include GI disturbances, postural hypotension, dyskinesias, and compulsive behaviors. Dopamine agonists are contraindicated in patients with psychosis, who require dopamine receptor blockers. Pramipexole and ropinirole are preferred over the ergot derivative bromocriptine due to their more limited adverse effect profile.

Selegiline, an **MAOI** that delays the metabolism of dopamine by monoamine oxidase B in the CNS, is used primarily as adjunctive therapy with L-dopa and carbidopa, generally in the later stages of Parkinson's disease. Its adverse effects are minimal, insomnia the most notable. It should not be taken with TCAs, SSRIs, or the opioid meperidine because of potential development of serotonin syndrome with CNS stimulation, hyperpyrexia, and coma.

Entacapone, a COMT inhibitor, is used as an adjunct to L-dopa and carbidopa to **reduce response fluctuations.** It is preferred over tolcapone, which is associated with hepatotoxicity. Other adverse effects of this class of drugs include GI disturbances, enhanced dyskinesias that may require a reduction in the dose of L-dopa, sleep disturbances, and an orange discoloration of the urine.

Amantadine may be beneficial early in the therapy of Parkinson's disease, possibly for only a few weeks before its effects wear off. It is also used as an adjunct to L-dopa and carbidopa. **Adverse effects** include **restlessness, insomnia, hallucinations, depression,** and, among many others, **livedo reticularis** (discoloration of the skin).

Muscarinic cholinoreceptor-blocking agents with some selectivity for CNS cholinoreceptors may be used alone to initially **diminish tremor and rigidity** (little

effect on bradykinesia). Their adverse effects are those typically described for this class of agents and include dry mouth, blurring of vision, mydriasis, urinary retention, as well as certain behavioral effects including drowsiness, confusion, and hallucinations. **They should be avoided in patients with angle-closure glaucoma and prostatic hypertrophy** and with other drugs that have muscarinic cholinoreceptor-blocking properties.

Structure

Bromocriptine is an ergot alkaloid derivative with activity at both dopamine D_1 and D_2 receptors. Pramipexole and ropinirole are nonergots with greater selectivity for dopamine D_2 receptors.

Mechanism of Action

L-dopa is decarboxylated in the striatum to dopamine, which interacts with postsynaptic dopamine D_2 receptors to activate inhibitory G-proteins (Gi) and inhibit adenylyl cyclase activity in GABAergic neurons.

Selegiline is a selective monoamine oxidase B inhibitor that delays the metabolism and prolongs the activity of the dopamine.

Entacapone inhibits the peripheral activity of the enzyme COMT to decrease the metabolism of L-dopa and thus increase its bioavailability and transport to the brain and prolong its duration of action. Tolcapone also inhibits COMT in the CNS, which reduces the metabolism of dopamine and prolongs its duration of action.

Amantadine's mechanism of action is unsure, but may be related to a change in the metabolism of dopamine that potentiates its action.

Muscarinic cholinoreceptor-blocking agents inhibit the activity of acetylcholine in the striatum, thus restoring some degree of balance between dopaminergic and cholinergic neurotransmission in the presence of reduced inhibitory levels of dopamine in patients with Parkinson's disease.

Pharmacokinetics

The absorption of L-dopa is rapid but is delayed by food and also by certain amino acids that compete for its transport in the GI tract and transport from blood to the brain. The concomitant administration of carbidopa decreases the peripheral metabolism of L-dopa by up to 80 percent.

COMPREHENSION QUESTIONS

17.1 A 56-year-old man is diagnosed with Parkinson's disease. Carbidopa is prescribed. This agent reduces which of the following?

A. The activity of decarboxylase in the CNS

B. The L-dopa dose necessary to achieve a therapeutic effect

C. The severity of L-dopa-associated dyskinesias

D. The time to onset of L-dopa's therapeutic effects

17.2 Which of the following is the most common limiting adverse effect of L-dopa?

A. Depression
B. Dyskinesia
C. Nausea
D. Orthostatic hypotension

17.3 Entacapone inhibits which of the following?

A. Dopamine D_2 receptors
B. COMT
C. Monoamine oxidase B
D. Muscarinic cholinoreceptors

ANSWERS

17.1 **B.** Carbidopa, which does not penetrate the brain, reduces peripheral dopa-decarboxylase activity, and the metabolism of L-dopa. The therapeutic effect of L-dopa can be achieved at a lower dose than would be possible without carbidopa.

17.2 **B.** The most common limiting adverse effect of L-dopa is dyskinesia that may occur in up to 90 percent of patients. Orthostatic hypotension, depression, and nausea are also adverse effects, but can be more readily managed and tolerated by patients.

17.3 **B.** Entacapone (and tolcapone) inhibits COMT. Selegiline inhibits monoamine oxidase B. Muscarinic cholinoreceptors are inhibited by biperiden and benztropine among others. Blockade of dopamine D_2 receptors would exacerbate the symptoms of Parkinson's disease.

PHARMACOLOGY PEARLS

- L-dopa may exacerbate symptoms in psychotic patients.
- In the absence of carbidopa, pharmacologic doses of pyridoxine (vitamin B_6) will increase the peripheral metabolism of L-dopa and thereby reduce its therapeutic effect.
- Signed patient consent is required for use of tolcapone, as is continuous evaluation of liver function.

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CASE 18

An 18-year-old male with past medical history of epilepsy since childhood presents via ambulance to the ER for status epilepticus. He has finally been stabilized by repeated doses of IV lorazepam. His mother states he had an unremarkable birth history, no prior head trauma, and negative head MRI in the past. He is noncompliant with his antiepileptic—phenytoin. His last seizure was 3 months ago, and usually is controlled if he takes his medication regularly. In the ER, patient is confused, is combative, but otherwise has a normal neurological and cardiovascular examination. There is also no evidence of any trauma. His initial labs including a blood count, comprehensive metabolic panel, and urine drug screen are negative. His phenytoin level is undetectable. You give him an IV loading dose of fosphenytoin and reorder his home oral dose.

- What is the mechanism of action of phenytoin?
- What are the major adverse effects of phenytoin?

ANSWERS TO CASE 18:
Antiseizure Drugs

Summary: An 18-year-old man presents with grand mal seizures and is given phenytoin.

- **Mechanism of action of phenytoin:** Blocks sodium channels and inhibits the generation of action potentials.
- **Adverse effects of phenytoin:** Common adverse effects include nystagmus, ataxia, confusion, hirsutism, and gingival hyperplasia. Rare but potentially fatal adverse effects include agranulocytosis (bone marrow failure) and Stevens-Johnson syndrome (fatal sever rash with skin shedding and mucosal involvement) and hepatotoxicity.

CLINICAL CORRELATION

Phenytoin has been widely used for the treatment of tonic-clonic (grand mal) seizures for over 60 years. It is also a major first-line drug used to treat partial seizures. It works by binding to and prolonging the inactive state of the Na^+ channel, thus blocking use-dependent Na^+ conductance and the generation of action potentials. It can be given orally, and its long half-life allows for once-a-day dosing. Phenytoin is metabolized in the liver by microsomal enzymes through parahydroxylation and glucuronide conjugation. Rates of oral absorption and metabolism can vary significantly from one patient to the next. At very low doses elimination is first-order; however, even within the therapeutic range, the liver enzymes responsible for its metabolism are near saturation, resulting in an increase in its half-life. Because of this inability to reach steady state and **phenytoin's low therapeutic index,** dosing of this drug must be individualized and plasma levels closely monitored. **Common side effects include nystagmus, ataxia, confusion, hirsutism, and gingival hyperplasia** in children (up to 50%). **Idiosyncratic reactions include skin rashes.** Its use should be avoided, if possible, during **pregnancy, because it is teratogenic. Phenytoin induces hepatic metabolism by microsomal enzyme induction** and can lower plasma levels of other drugs. Phenytoin's level can be increased by drugs that inhibit its hepatic metabolism. Caution and close monitoring of blood levels of phenytoin must be undertaken when phenytoin is used in combination with other drugs.

APPROACH TO:
Pharmacology of Antiseizure Agents

OBJECTIVES

1. List the major antiseizure agents.
2. Describe the mechanism of action of major antiseizure agents.

3. List and discuss the common adverse effects and toxicities of major antiseizure agents.
4. List the therapeutic uses of major antiseizure agents.

DEFINITIONS

Seizure: A nonrecurrent abnormal discharge from the brain.

Epilepsy: A chronic dysfunction of recurrent seizures.

Therapeutic index: A measure of the relationship (ratio) between the dose necessary to produce a therapeutic effect, usually expressed as the median effective dose (ED_{50}), and the dose necessary to produce an undesired effect, usually expressed as the median toxic dose (TD_{50}).

First-pass effect: The extensive metabolism by the liver of many drugs administered orally that may limit bioavailability to such an extent that an effective therapeutic dose cannot be achieved.

DISCUSSION

Class

Several classes of drugs are available for the treatment of seizures (Table 18–1). Mechanisms of action of these drugs include those that inhibit voltage-dependent Na^+ channels by extending their inactive state (**phenytoin, carbamazepine, oxcarbazepine, lamotrigine**), those that affect T-type calcium channels (**ethosuxemide**), those that enhance γ-aminobutyric acid (GABA) neurotransmission (**benzodiazapines, phenobarbital**), drugs with multiple mechanisms of action (**valproic acid, topiramate**), and those that have other mechanisms of action (**gabapentin, levetiracetam**).

In addition to phenytoin, **carbamazepine** is another major first-line antiseizure drug used to treat both partial seizures and generalized tonic-clonic seizures. Serum levels of carbamazepine must be monitored closely, especially early in therapy because this drug induces hepatic enzymes responsible for its metabolism and thus blood levels will fall over time. **Drowsiness, diplopia, and ataxia are common side effects.** GI disturbances, headache, dizziness, and sedation are also not uncommon (Table 18–1). **Idiosyncratic reactions include serious skin rash** (Stevens-Johnson syndrome) and rarely a **fatal aplastic anemia**. Carbamazepine is also used therapeutically to treat bipolar disorder and trigeminal neuralgia. **Oxcarbazepine** was developed from carbamazepine to overcome the problems with induction of hepatic metabolic enzymes. Its side effects are similar to carbamazepine, except it is more likely to produce significant hyponatremia. **Limotragine** is also commonly used for treatment of seizures. Blood levels must also be monitored because it is influenced by the presence of hepatic P450 enzymes. Common side effects include rash, somnolence, and nausea. Limotragine is also used in the treatment of bipolar depression.

Ethosuxemide is only used in the treatment of absence seizures and is not effective in other types of seizures. Adverse effects include nausea and somnolence.

Table 18–1 • SELECTED ANTISEIZURE AGENTS AND ADVERSE EFFECTS

Agent Selected	Adverse Effects
Na^+ Channel Inhibitors	
Phenytoin	Nystagmus, ataxia, confusion, hirsutism, gingival hyperplasia in children (up to 50%), idiosyncratic reactions (eg, skin rashes), teratogenicity
Carbamazepine	Drowsiness, diplopia, ataxia, GI disturbances, headache, dizziness, sedation, idiosyncratic reactions (skin rash, aplastic anemia)
Oxcarbazepine	Nausea, rash, hyponatremia, sedation, headache, dizziness, vertigo, ataxia, diplopia
Lamotrogine	Rash, nausea, dizziness, diplopia
T-type Calcium Channel Inhibitors	
Ethosuximide	GI disturbances
GABA Enhancers	
Benzodiazapines	Sedation, addiction, falls, tolerance
Phenobarbital	Nausea, rash, sedation, lethargy, ataxia, tolerance, dependence
Multiple Mechanisms	
Valproic acid	Idiosyncratic hepatotoxicity
Topiramate	Weight loss, cognitive disturbance
Unknown Mechanisms	
Gabapentin	Somnolence, ataxia
Levetiracetam	Fatigue, somnolence anxiety

Benzodiazepines are used only in acute settings or as an adjunct to therapy due to the development of tolerance to these drugs. Side effects include sedation, irritability, and falls. Lorazepam and diazepam are frequently used to treat acute seizures in the hospital setting.

Phenobarbital is an older drug used for treating partial and generalized tonic-clonic seizures. Although it can be used in the hospital setting, its use is limited by its potential for addiction and drug-drug interactions.

Valproic acid, like ethosuximide, is used to treat generalized **absence** seizures. However, because of the potential for an **idiosyncratic hepatotoxicity,** it is reserved for patients with concomitant generalized tonic-clonic seizures. It is also used to control myoclonic seizures and for the treatment of bipolar disorder and for prophylaxis of migraine headache. Its use in pregnancy is associated with an increased risk of **neural tube defects.**

Similar to **phenytoin,** the **therapeutic index for these drugs is low.** Thus, serum drug levels need to be carefully monitored.

Use of **topiramate** is associated with weight loss and impaired cognition, both of which are dose-related effects. **Gabapentin** and **levetiracetam** are used as an add-on therapy, with the advantage that both are well tolerated and have no known drug-drug interactions.

Mechanism of Action

P**henytoin, carbamazepine, oxcarbazepine,** and **lamotrigine** share a common mechanism of action, the inhibition of neurotransmission through the prolongation of the inactive state of voltage-dependent Na^+ channels.

Ethosuximide reduces low threshold T-type Ca^{2+} current in the thalamus that appears to provide pacemaker activity responsible for cortical generation of absence seizures.

Valproic acid and **topiramate** have more than one mechanism of action including an effect on Na^+ channels, blockade of NMDA receptors, and increased activity of the neurotransmitter GABA. The benzodiazepines, diazepam and lorazepam, potentiate GABA neurotransmission.

Mechanisms of action of **gabapentin** and **levetiracetam** are not understood.

Administration

Phenytoin, valproic acid, benzodiazepines, and phenobarbital are available for both oral and parenteral (IV) administration. Because phenytoin may precipitate at its site of injection, it has been replaced for intravenous injection by the more water-soluble fosphenytoin, which is only available for parenteral administration.

Carbamazepine, ethosuximide, gabapentin, levetiracetam, and topiramate are only available for oral administration. Both phenytoin and carbamazepine exist also in extended-release preparations. Valproic acid is hydroscopic and therefore is available for oral administration as a capsule in corn oil or, for pediatric use, in syrup. It is also available as a more patient preferred enteric-coated tablet formulated as divalproex sodium, which is a 1:1 compound of valproic acid and sodium valproic acid. It is also available for parenteral use.

Pharmacokinetics

Because phenytoin's liver metabolic enzymes become saturated at a low dose, relatively small changes in the dose can lead to very large changes in the plasma concentration and, thus, the development of toxicity.

With continuous administration, carbamazepine induces the synthesis of liver microsomal enzymes responsible for its own metabolism resulting in a substantially decreased half-life requiring significant dose adjustment. Through the same induction mechanism, carbamazepine can also alter the metabolism of a number of other drugs. Likewise, there are a number of drugs that can alter the metabolism of carbamazepine by induction of the appropriate microsomal enzymes. Oxcarbamazepine is a closely related anticonvulsant that is less likely to induce microsomal enzyme synthesis.

Valproic acid inhibits its own metabolism and the metabolism of other drugs, including phenytoin. It displaces phenytoin from its binding to plasma proteins.

COMPREHENSION QUESTIONS

18.1 Blockade of T-type calcium currents is the major mechanism of action for which of the following drugs used to manage seizures?

A. Carbamazepine
B. Diazepam
C. Ethosuximide
D. Phenytoin

18.2 Which of the following drugs used to manage seizures requires a significant dose adjustment with continuous administration?

A. Carbamazepine
B. Diazepam
C. Ethosuximide
D. Phenytoin

18.3 For which of the following drugs used to manage epilepsy does a small change in its bioavailability result in a disproportionate increase in its blood levels and toxicity?

A. Carbamazepine
B. Diazepam
C. Ethosuximide
D. Phenytoin

ANSWERS

18.1 **C.** The anticonvulsant activity of ethosuximide when used to treat absence seizures is due to its blockade of T-type calcium currents in the thalamus. Carbamazepine and phenytoin, which are not used to treat absence seizures, block sodium channels. Diazepam, which is not a first-line drug for absence seizures, potentiates GABA neurotransmission.

18.2 **A.** Carbamazepine induces the synthesis of liver microsomal enzymes responsible for its own metabolism, necessitating a significant dose adjustment with its continued administration.

18.3 **D.** A small change in the bioavailability of phenytoin may result in a disproportionate increase in its blood level because its metabolic enzymes become saturated even at therapeutic doses.

PHARMACOLOGY PEARLS

- Currently available antiseizure drugs control seizures in about 80 percent of patients with epilepsy.
- Antiseizure drugs increase the risk of congenital malformations, including the "fetal hydantoin syndrome" (phenytoin) and spina bifida (valproic acid).
- Hepatic metabolic enzyme levels are frequently altered by these drugs, resulting in a low therapeutic index, and therefore blood levels of antiseizure medications must be closely monitored.

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CASE 19

An 18-year-old man is brought into the emergency department after being found on the street unresponsive. He is lethargic and does not answer questions. He has been given 1 ampule of Dextrose intravenously without result. On examination, his heart rate is 60 beats per minute, and respiratory rate is 8 per minute and shallow. His pupils are pinpoint and not reactive. There are multiple intravenous track marks on his arms bilaterally. The emergency physician concludes that the patient has had a drug overdose.

- What is the most likely diagnosis?
- What is the most appropriate medication for this condition?
- In addition to its therapeutic actions, what other effects might this medication produce?

ANSWERS TO CASE 19:
Opioid Overdose

Summary: An 18-year-old unresponsive man presents with pinpoint pupils, shallow respirations, and multiple intravenous track marks on his arms bilaterally.

- **Most likely diagnosis:** Opioid overdose, likely heroin.
- **Most appropriate medication for this condition:** Naloxone.
- **Additional effects this medication might produce:** Symptoms of precipitated withdrawal that may include lacrimation, rhinorrhea, sweating, dilated pupils, diarrhea, abdominal cramping, and tremor.

CLINICAL CORRELATION

Opioids are drugs with morphine-like activity that reduce pain and induce **tolerance** and **physical dependence.** Certain individuals seek the euphoria obtained from the intravenous injection of opioids such as heroin. There are three different cell **receptors** specific for opioids: **mu, kappa, and delta** (μ, κ, δ), all of which exist as multiple subtypes. This patient has the classic signs of **opioid overdose: somnolence, respiratory depression, and miosis.**

Stimulation of the mu receptor results in analgesia (supraspinal and spinal), respiratory depression, euphoria, and physical dependence. Continuous, heavy use of opioids can result in tolerance, where more drug is required to obtain the same euphoric "high," and also to physical dependence. Naloxone, a competitive antagonist of opioids, is used to treat opioid overdose. Its intravenous administration leads to an almost immediate reversal of all effects of the opioids.

In individuals who are physically dependent, administration of naloxone will immediately precipitate **opioid withdrawal,** which consists of a constellation of signs and symptoms that include nausea and vomiting, muscle aches, lacrimation or rhinorrhea, diarrhea, fever, and dilated pupils. Likewise, when someone physically dependent on opioids ceases its administration, there is a more slowly developing (hours or days) constellation of symptoms of opioid withdrawal that includes **sensitivity to touch and light, goose flesh, autonomic hyperactivity, GI distress, joint and muscle aches, yawning, salivation, lacrimation, urination, defecation, and a depressed or anxious mood.** In general, physical dependence induced by opioids with a short half-life tends to result in a rapid severe withdrawal, while physical dependence induced by opioids with a long half-life tends to be associated with a less severe and more gradual course of withdrawal. Although very uncomfortable, opioid withdrawal is **generally not life-threatening.**

The opioid methadone may be administered in a daily dose to individuals physically dependent on opioids, most notably heroin, as a "maintenance therapy" or to ameliorate the symptoms of opioid withdrawal. Only specialists licensed in addition can prescribe methadone for this purpose.

APPROACH TO:
Pharmacology of the Opioids

OBJECTIVES

1. Describe the mechanism of action of opioids as analgesics.
2. Explain how opioids reduce pain.
3. List the major opioid agonists and antagonists, their therapeutic uses, and their important pharmacokinetic properties.
4. Describe the adverse effects of opioids.

DEFINITIONS

Addiction: The persistent, compulsive continuation of a behavior or use of a chemical substance despite its adverse physiological, psychological, or social effects.

Drug tolerance: Decreased response to a drug with its continued administration that can be overcome by increasing the dose. A cellular tolerance develops to certain drugs of abuse that act on the CNS because of a poorly understood biochemical or homeostatic adaptation of neurons to the continued presence of the drug. Also, in addition to a cellular tolerance, a metabolic tolerance can develop to the effects of some drugs because they increase the synthesis of enzymes responsible for their own metabolism (alcohol, barbiturates).

Drug dependence: Continued need of the user to take a drug. Psychologic dependence is the compulsive behavior of a user to continue to use a drug no matter the personal or medical consequences. Inability to obtain the drug activates a "craving" that is very discomforting. Physical or physiologic dependence is a consequence of drug abstinence after chronic drug use that results in a constellation of signs and symptoms that are often opposite to the initial effects of the drug and to those sought by the user. Psychologic dependence generally precedes physical dependence but, depending on the drug, does not necessarily lead to it. The development of physical dependence, the degree of which varies considerably for different drugs of abuse, is always associated with the development of tolerance, although the exact relationship is unclear.

Endogenous opioid peptides: Class of natural endogenous peptides that bind to human mu, delta, and kappa opioid receptors. Four classes of such peptides have been described: (1) the pentapeptide enkephalins (met and leu), (2) the endorphins (β-endorphin), (3) the dynorphins (A, B, C), all of which are proteolytically released from larger precursor molecules, and (4) the endomorphins. Together, they may modulate a number of important functions of the body (eg, pain, reactions to stress and anxiety).

Fasciculation: Muscular twitching of contiguous groups of muscle fibers.

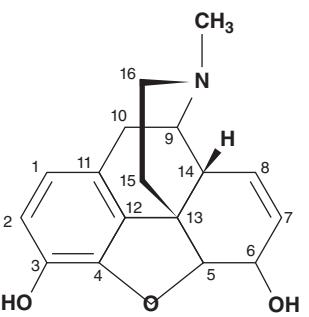
Lacrimation: Secretion of tears from the eyes.

Rhinorrhea: Mucous-like material that comes out of the nose.

DISCUSSION

Class

Morphine, the prototype opioid, is derived from opium, a crude material obtained from the seed pod of the opium poppy plant. The chemical structure of morphine is shown in Figure 19–1. Many other derivatives of the opium plant (opiates) and other drugs with similar effects (opioids) have been discovered or synthesized. Chemical modifications of the morphine structure results in significant alterations in potency and in the ratio of agonist to antagonist effects (Table 19–1). However, no major improvement in the analgesic effect of this class of opioids has been achieved; morphine is still one of the most widely used opioids. The opioids are classified in several ways: (1) **strength** of **analgesic** effect (strong and weak agents); (2) ratio of **agonist to antagonist effects** (pure agonists, mixed agonist-antagonists, and antagonists), and (3) **actions** (analgesic, antitussive, and antidiarrheal drugs). The major therapeutic application for morphine and other **strong opioids** (eg, **fentanyl, hydromorphone, methadone**) is the management of moderate to severe pain (eg, pain associated with trauma, burns, cancer, acute myocardial infarction, and renal or



	Ring Position			
	3[a]	6[b]	17[c]	Substitution
Morphine	–OH	–OH	$–CH_3$	Prototype
Codeine[d]	$–OCH_3$	–OH	$–CH_3$	Methylmorphine
Heroin[e]	$–OCOCH_3$	$–OCOCH_3$	$–CH_3$	Diacetyl morphine
Naloxone[f]	–OH	=O	$–CH_2CH{=}CH_2$	Allyl
Thebaine[g]	$–OCH_3$	$–OCH_3$	$–CH_3$	Dimethyl morphine

[a]Substitutions at the C-3 phenolic position and the C-6 hydroxyl position of morphine.
[b]Modification of the methyl group on the nitrogen in the piperidine ring (N-17).
[c]Methyl substitution: decreased first-pass effect, increased oral absorption in the brain to morphine.
[d]Allyl substitution: antagonist.
[e]Dimethyl substitution: convulsant.

Figure 19–1. Structure-activity relationships of opioids.

Table 19–1 • SELECTED OPIOIDS

Strong Opiods Agonists	Notes
Morphine (also hydromorphone, oxymorphone, heroin)	See case description Heroin is metabolized to morphine
Methadone	Indications are similar to morphine. Used to treat difficult to manage pain (eg, cancer, neuropathic pain). Used as an oral opioid substitute to treat opioid dependence. Its long duration of action and slow metabolism result in less severe withdrawal than with other shorter acting opioids.
Fentanyl (also alfentanil, sufentanil, remifentanil)	Has a shorter duration of action than morphine. Available for parenteral use only. Used as a preanesthetic medication and for pre- and postoperative pain. Fentanyl (or morphine) is used to supplement the analgesia and sedative-hypnotic effects of nitrous oxide and halothane equals "balanced anesthesia." Rapid IV administration of high doses may cause severe truncal muscle rigidity that can be reversed by naloxone. Available as a transdermal patch and lozenge.
Meperidine	Although still used, in overdose meperidine may cause CNS excitation (tremors, delirium, and hyperreflexia) and seizures as a result of formation of an *N*-demethylated metabolite, normeperidine. With MAOIs may cause severe restlessness, excitement, fever, and seizures (serotonin syndrome). It has weak anticholinergic activity that may result in mydriasis (not miosis) and tachycardia. Meperidine has weak or no effect on the cough reflex.
Codeine (also oxycodone, hydrocodone, dihydrocodeine)	Used for moderate pain. Has good bioavailability by the oral route (compared to morphine); 10% converted to morphine. Causes little respiratory depression and less dependence liability than morphine. An overdose may cause seizures. Codeine and other weak opioid agonists are often used in combination with other analgesics such as aspirin (Percodan) or acetaminophen (Percocet).
Weak Opioid Agonists	**Notes**
Diphenoxylate, Loperamide	Used for the symptomatic treatment of diarrhea. Insolubility of diphenoxylate limits its absorption across the GI tract. Loperamide does not cross the blood-brain barrier. Minimal dependence liability or other centrally mediated opioid effects. To limit its parenteral use, diphenoxylate is only available combined with atropine.
Mixed Opioid Agonistantagonists/Partial Agonists	
Buprenorphine (also pentazocine, nalbuphine, butorphanol, dezocine, tramadol)	Buprenorphine is a slowly dissociating partial agonist at the μ-opioid receptor. Its agonist actions are resistant to naloxone reversal. It is used primarily for heroin detoxification. It has less dependence liability than morphine. At higher doses it has antagonist activity at the μ-opioid receptor, which limits its ability to cause respiratory depression.
Opioid Antagonists	
Naloxone and Naltrexone (also nalmefene)	Competitive antagonists at opioid receptors, which can precipitate opioid withdrawal. Naloxone is administered IV because of poor oral absorption. It is used to treat acute opioid overdose. Because of its short duration of action, multiple dosing may be necessary. Naltrexone is FDA approved for use in chronic alcoholics to reduce craving for alcohol.

biliary colic). **Weaker opioids** such as **codeine** and **pentazocine** are used to manage mild to moderate pain. Other important therapeutic uses include the management of **diarrhea** (eg, **codeine, diphenoxylate, loperamide**), dyspnea associated with pulmonary edema secondary to acute left ventricular failure, suppression of the cough reflex (codeine), and maintenance and withdrawal therapy for opioid dependence (**methadone, buprenorphine**). The antitussive (cough suppressant) action and antidiarrheal action of the opioids are at least partially separable from their analgesic action. Separate drugs have been developed to exploit these effects.

The sites of opioid action include areas in the central nervous system (CNS) where they **raise the threshold to pain** (ie, decrease the sensation of pain) including (1) the ***spinal cord,*** where opioids act directly on **receptors** on the **terminals of primary afferent sensory neurons** in the **dorsal horn of the spinal cord** to inhibit release of excitatory transmitters like **substance P,** (2) the ***thalamus,*** where opioids act on **ascending pathways** to **directly inhibit pain transmission from the spinal cord to higher centers of the brain** (via the spinothalamic tract and spinoreticular tract), and (3) the ***midbrain*** periaqueductal gray area and rostral ventral medulla (nucleus raphe magnus), where opioids **activate descending *inhibitory* neurons to the spinal cord,** thus preventing pain transmission. Opioids also act on the cerebral cortex, amygdala, and hippocampus to decrease the emotional reactivity to pain (ie, decrease the perception of pain). There is also a direct inhibitory effect of opioids on sensory nerve endings. In addition to the CNS, opioids also act on other organs including, notably, the GI tract and kidney.

The most commonly observed effects when the opioids are used for the relief of pain are **sedation, nausea and vomiting, and constipation.** Large doses regularly induce **respiratory depression and euphoria** or mental clouding. The major adverse effects of selected opioids are presented in Table 19–2. Methadone can cause potentially fatal QTc prolongation.

Tolerance to some effects of the opioids (Table 19–3) occurs gradually (days) with repeated administration such that a larger dose is necessary to produce the same initial effect. The tolerance is because of a direct action of opioids on neurons (ie, cellular tolerance) rather than to an increase in their metabolism (metabolic tolerance). Tolerance does not occur to all the effects of the opioid agonists or to the action of antagonists (see Table 19–3). Tolerance to one opioid agonist can confer tolerance to other opioid agonists, that is, cross-tolerance. However, there is no cross-tolerance between opioid agonists and other nonopioid drugs that act on the CNS, such as the benzodiazepines, barbiturates, ethanol, and stimulants.

Opioid-induced **respiratory depression** may be potentiated in the presence of sedative-hypnotic agents, antipsychotic agents, or antidepressant agents. Opioids, particularly **meperidine,** may interact with MAOIs (tranylcypromine, phenelzine) to cause **serotonin syndrome.**

Structure

Opioids may be full agonists (eg, morphine, heroin) or partial agonists (eg, buprenorphine, pentazocine). Morphine is a phenanthrene alkaloid with a phenylmethyl-piperidine ring structure. Simple chemical substitutions can markedly alter its pharmacologic properties (see Figure 19–1).

Table 19–2 • ADVERSE EFFECTS OF OPIOIDS

Adverse Effect: Cause	Notes
Respiratory depression (major limiting effect) caused by direct inhibition of respiratory center in the brain stem results in decreased sensitivity tohypoxic drive by carbon.	Occurs at therapeutic doses of morphine. Tolerance develops that parallels tolerance to analgesia. Respiratory depression is generally not a serious clinical problem except in several special circumstances where opioids may be contraindicated: (1) decreased respiratory reserve (eg, dioxide, emphysema, obstructive lung disease); (2) head injury or CNS tumors; and (3) pregnancy (to avoid fetal respiratory depression). Respiratory depression is a serious and potentially fatal consequence of opioid overdose.
Sedation/drowsiness	A decreased ability to concentrate. Ambulatory patients and elderly are at risk for accidents. A paradoxical dysphoria and increased anxiety may occur in children and women.
Nausea (30%), vomiting (10%): Caused by direct stimulation of the CTZ in the area postrema of the medulla, which activates the vomiting center.	More likely to occur in ambulatory patients. Self-limiting with continued administration because of subsequent direct inhibition by morphine of the vomiting center.
Dependence	See Clinical Correlation, Case 19.
Pneumonia: May result from inhibition of cough reflex.	Increased likelihood in patients whose respiration is already seriously compromised.
Miosis: Stimulation of the Edinger-Westphal nucleus of the oculomotor nerve (III) results in contraction of the pupillary sphincter with constriction of the pupils ("pinpoint" pupils).	Occurs at therapeutic doses. Pupils do not dilate, even in the dark. Parasympathetic pathways involve release of ACh in the ciliary ganglion; miosis can be blocked by atropine. Sign of opioid (eg, heroin) overdose.
Hypotension: Opioids inhibit the (tonically active) vasomotor center in the brain stem to cause some peripheral arterial and venous vasodilation.	Usually not a clinical problem but is a relative contraindication for patients in shock or who have low blood pressure or who are hypovolemic (reduced blood volume). The elderly are particularly susceptible.
Adverse Effects of Opioids (Generally Extensions of Pharmacologic Activity)	
Constipation (delayed fecal movement/ increased absorption of water): Mechanism is uncertain, but probably due to peripheral action on the enteric nervous system to inhibit acetylcholine release. Effect is to increase GI tone with a concomitant decrease in coordinated propulsive activity and motility. Opioids also increase anal sphincter tone and decrease attention to the defecation reflex.	A major complaint of patients receiving opioids for analgesia. There is no clinically significant tolerance in humans. Stool softeners are used to treat (mineral oil/glycerin suppositories).
Urine retention: Opioids decrease urinary output due to decreased renal plasma flow, possible increased release of ADH from pituitary, decreased coordinated contractility of the ureters and bladder, increased urethral sphincter tone, and inattention to the urinary reflex.	Usually not a clinical problem except in patients with enlargement of the prostate. Catheterization may be necessary. More common in elderly. Increased tone of the ureters may result in a paradoxical increase in pain. A similar effect may occur when opioids are used to treat the pain of biliary colic.

Table 19–3 • ADVERSE EFFECTS BASED ON RELATIVE TOLERANCE TO OPIOIDS

Substantial	Minimal
Analgesia	Constipation
Respiratory depression	Seizures (meperidine, codeine)
Euphoria	Antagonist activity (naloxone, naltrexone)
Sedation	Miosis
Nausea and vomiting	

Mechanism of Action

Opioid agonists bind to G-protein-coupled neural receptors (**mu, delta, kappa**) to **reduce adenylyl cyclase activity,** to reduce presynaptic calcium conductance, which causes a decrease in neurotransmitter release, and to enhance postsynaptic potassium conductance, which causes a decrease in cell responsiveness to excitatory neurotransmitters.

Administration

Opioids are usually administered orally, but some like morphine can also be administered rectally or parenterally.

Specialized administration

Patient-controlled analgesia (PCA): By infusion (morphine/meperidine/hydromorphone).

Regional analgesia: Epidural route is favored because it produces fewer adverse effects. They may also be administered into subarachnoid or intrathecal spaces. There may be delayed respiratory depression, nausea, and vomiting that can be reversed with naloxone.

Transdermal fentanyl patch: Used for chronic pain

Buccal fentanyl lozenge/lollipop

Butorphanol nasal spray

Narcotic combinations with acetaminophen and NSAIDs

Pharmacokinetics

Most opioids are absorbed well. Morphine, given orally, shows variable but significant first-pass metabolism (glucuronide conjugation) with a low oral to parenteral potency ratios (25%). It is usually given parenterally. Codeine and methadone are well absorbed after oral administration (approximately 60%) because of limited first-pass metabolism.

All opioids are metabolized by the liver. Metabolism usually results in more polar metabolites and frequently involves conjugation of the phenolic hydroxyl with glucuronic acid. Excretion is primarily by way of the kidneys. In addition to inactive metabolites, morphine is conjugated in the liver to morphine-3-glucuronide, which has neuroexcitatory properties. Morphine is also metabolized (10%) to

morphine-6-glucuronide, which at high levels has analgesic potency greater than morphine itself. Codeine and heroin are metabolized to morphine. Heroin is also metabolized to morphine. Meperidine is metabolized to normeperidine that causes seizures in patients where it accumulates. For this reason, its use is discouraged.

The fetal blood-brain barrier is readily crossed by the opioids, and infants born to mothers given (or self-administering) large doses of opioids may have severe respiratory depression.

COMPREHENSION QUESTIONS

19.1 A 25-year-old man underwent surgery for an inguinal hernia. Postoperatively, he receives intravenous morphine sulfate for his pain. Morphine produces analgesia through which of the following actions?

A. Activation of neuronal adenylyl cyclase
B. Increased presynaptic neurotransmitter release
C. Reduction of postsynaptic neuronal potassium conductance
D. Reduction of presynaptic neuronal calcium conductance

19.2 Which of the following opioid agonists is not metabolized to an active agent with analgesic activity?

A. Morphine
B. Codeine
C. Heroin
D. Meperidine

19.3 QTc prolongation is a potentially fatal adverse effect associated with which opioid?

A. Methadone
B. Hydrocone
C. Fentanyl
D. Morphine

ANSWERS

19.1 **D.** Opioid agonists bind to G-protein-coupled receptors to reduce adenylyl cyclase activity, to reduce presynaptic calcium conductance, which results in a decrease in neurotransmitter release, and to enhance postsynaptic potassium conductance, which results in decreased responsiveness to excitatory neurotransmitters.

19.2 **D.** Meperidine is metabolized to normeperidine that may result in seizures. Morphine is metabolized to morphine-6 glucuronide. Codeine and heroin are metabolized, in part, to morphine.

19.3 **A.** Potentially fatal QTc prolongation is a side effect unique to methadone. ECG monitoring is important during its therapeutic use.

PHARMACOLOGY PEARLS

- Seeking the relief of pain is one of the most common reasons for patient visit.
- Prescription drug abuse is a growing problem, and accidental deaths from use of oxycodone, hydrocodone, and morphine, among others, are increasing.
- Seizures may occur in patients with renal failure because of the action of the morphine metabolite morphine-3-glucuronide.
- Treatment of chronic, noncancer pain using opioids remains controversial. However, treatment of acute pain, or pain in patients with a terminal illness, is generally medically necessary.

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CASE 20

A 22-year-old woman is brought into the emergency department via ambulance because of a suicide attempt. Soon after a "night on the town," she called her boyfriend saying that she took a handful of sleeping pills. On examination, she appears lethargic, but groans and moves all her extremities to painful stimuli. Her blood pressure is 110/70 mm Hg, heart rate is 80 bpm, and oxygen saturation is 99 percent. Her pupils are of normal size and reactive to light. Her deep tendon reflexes are normal bilaterally. In the field, she was given an intravenous bolus of dextrose and an ampule of naloxone without response. Her boyfriend, with whom she had an argument, brings in the bottle of sleeping medication, which reads "lorazepam."

- What is the danger of an overdose with this class of medication?
- What is the cellular mechanism of action of this class of medication?
- What pharmacologic agent can be used to treat this patient, and what is its mechanism of action?

ANSWERS TO CASE 20:
Benzodiazepines

Summary: A 22-year-old woman is brought to the emergency department because of a suicide attempt overdose with lorazepam. She is hemodynamically stable, has no focal neurologic deficits, but is lethargic. Intravenous dextrose and naloxone have been given without response.

- **Danger of an overdose with this class of medication:** Lorazepam is a benzodiazepine that belongs to a class of agents known as sedative-hypnotics that can depress the activity of the central nervous system (CNS). An overdose of a benzodiazepine, particularly in the presence of another CNS depressant like alcohol, can lead to sedation, hypotension, respiratory depression, coma, and death. Benzodiazepine overdose, without alcohol or other depressant agents, is rarely fatal.
- **Cellular mechanism of action of lorazepam:** Binds to a distinct benzodiazepine receptor site on the γ-aminobutyric acid (GABA) receptor–chloride channel complex to allosterically increase the affinity for and frequency of GABA interactions with neuronal $GABA_A$ receptors.
- **Pharmacologic agent used to treat benzodiazepine overdose and its mechanism of action:** Flumazenil is a competitive antagonist at benzodiazepine receptors. It is used clinically to reverse the symptoms of benzodiazepine overdose.

CLINICAL CORRELATION

This 22-year-old woman had likely been drinking, and subsequently ingested numerous tablets of lorazepam, a benzodiazepine; she exhibits the **classic signs of overdose: drowsiness, confusion, and amnesia.** In general, an overdose of benzodiazepines is not fatal, which is a major advantage over previous classes of drugs used for their sedative-hypnotic properties, such as the barbiturates. Symptoms of benzodiazepine overdose may include **drowsiness, confusion, amnesia, hypotension,** and, in the absence of compromised pulmonary function, **mild respiratory depression.** However, in the presence of other sedative-hypnotic agents like ethanol, which is suspected in this case, there may be **enhanced sedation** and respiratory depression that can result in **coma and even death.**

APPROACH TO:
Benzodiazepines

OBJECTIVES

1. Describe the mechanism of action of benzodiazepines.
2. Examine chronic use of benzodiazepines.
3. Identify the withdrawal symptoms of this class of drugs.

DEFINITIONS

$GABA_A$ receptor–chloride channel complex: A multi-unit protein that interacts with GABA to regulate chloride conductance. This action can be modified by the allosteric interaction of other substrates, such as the benzodiazepines and barbiturates.

Allosteric interaction: A conformational change of a protein ($GABA_A$ receptor–chloride channel complex) caused by noncompetitive binding of a substrate (benzodiazepine) at a site other than the active site of that protein.

DISCUSSION

Benzodiazepines are drugs used to treat a variety of disorders including, most notably, anxiety and insomnia, as well as seizures. They are also used clinically as muscle relaxants, as preanesthetic medications, and as amnestic agents for short medical and surgical procedures (Table 20–1).

Chronic use (weeks) of the benzodiazepines can result in **tolerance** (a decreased response with continued drug administration) and **physical dependence** with an identifiable **withdrawal syndrome** that includes **severe anxiety and insomnia** and less frequently, as seen with alcohol **withdrawal, tremulousness, tachycardia, hypertension, hallucinations, and seizures** that **can be life threatening.** Withdrawal from shorter acting and intermediate-acting benzodiazepines occurs more quickly and is more severe than from longer acting drugs, and is usually managed with tapered dose reduction of the drug. Alternatively, because of the phenomenon of cross-tolerance, benzodiazepines with longer half-lives (eg, diazepam) can be substituted for shorter acting benzodiazepines or other sedative-hypnotic drugs, like ethanol and the barbiturates, to stabilize the patient and to reduce the severity of the withdrawal syndrome.

Zolpidem, zaleplon, and eszopiclone are structurally different than the benzodiazepines but have a similar mechanism of action. They are widely used for the short-term management of insomnia. They have few of the other actions of the benzodiazepines and are less likely to cause physical dependence and drug abuse.

Table 20–1 • SELECTED CLINICAL USES OF BENZODIAZEPINES

Anxiety disorders
Insomnia
Convulsive disorders
Acute status epilepticus
Presurgical administration to reduce anxiety and for amnestic effects
Spastic disorder or muscle spasm
Involuntary movement disorder (such as restless leg syndrome)
Detoxification from alcohol
Psychiatric conditions (eg, acute mania, impulse control disorders)

Flumazenil, a competitive inhibitor of the benzodiazepine-binding site on the $GABA_A$ receptor–chloride channel complex, will quickly reverse the effects of the benzodiazepines. In dependent individuals it can induce symptoms of withdrawal. It is used to treat significant CNS depression because of benzodiazepine overdose such as in this clinical case.

Mechanism of Action

Like the barbiturates (another class of sedative-hypnotic agents), the benzodiazepines bind to the **$GABA_A$ receptor–chloride channel complex** (Figure 20–1). However, unlike the barbiturates, which increase the *duration* of GABA-mediated chloride channel opening, the benzodiazepines bind to a different site and act to increase the affinity of the complex for GABA. This results in **increased chloride conductance resulting in neuronal hyperpolarization.** Because GABA is the principal inhibitory neurotransmitter of the brain, its increased action, facilitated by a benzodiazepine, will lead to a reduced neuronal stimulation by excitatory neurotransmitters. The outcome, among others, is sedation and hypnosis.

Zolpidem, zaleplon, and eszopiclone act on a subtype of the benzodiazepine receptor (BZ1) and, like the benzodiazepines, reduce chloride conductance in the CNS.

Flumazenil competitively inhibits the action of benzodiazepines at their receptors on the GABA receptor–chloride channel complex.

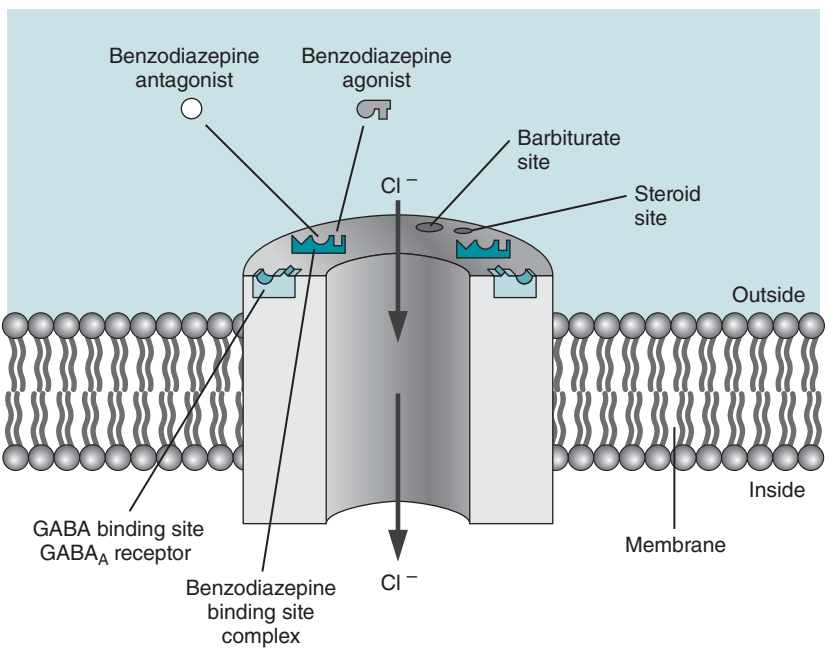

Figure 20–1. Chloride channel showing benzodiazepine receptor on cell membrane. (Used, with permission, from Toy EC, Klamen DL. Case Files: Psychiatry, 2nd ed. New York: McGraw-Hill, 2007:409.)

Pharmacokinetics

Benzodiazepines are well absorbed from the GI tract, although clorazepate, a prodrug, is first decarboxylated in gastric juice to the long-acting (>50 hour) **active metabolite *N*-desmethyldiazepam.** Because the lipid solubility of the benzodiazepines varies more than 50-fold, there is considerable variation in their onset of action (diazepam, midazolam > lorazepam, clonazepam, alprazolam > oxazepam, temazepam).

Under most circumstances, the duration of action of the benzodiazepines (Table 20–2) is related to their biotransformation by *Dealkylation* to the long acting (>50 hours) active metabolites desmethyldiazepam (eg, diazepam, chlordiazepoxide) or desalkylflurazepam (flurazepam).

Oxidation to short- or intermediate-acting metabolites (alprazolam, triazolam).

Rapid conjugation to metabolites with no intrinsic activity (eg, oxazepam, lorazepam).

Clearance of the benzodiazepines is **decreased significantly in the elderly,** or in patients with **liver disease**. Thus these populations should, in general, be administered reduced dosages. **Elderly patients** may also be susceptible to **paradoxical agitation** and insomnia. The benzodiazepines should be **avoided in pregnancy** because **neonates may develop withdrawal symptoms.**

Table 20–2 • SELECTED BENZODIAZEPINES

Benzodiazepine	Onset of Action	Half-Life of Parent (Hours)	Half-Life of Metabolite (Hours)	Comparative Oral Dose
Short Acting				
Midazolam	Rapid IV	0.5–1	Inactive	None
Triazolam	Intermediate	1–4	Inactive	0.5 mg
Intermediate Acting				
Alprazolam	Intermediate	6–20	Inactive	0.5 mg
Clonazepam	Intermediate	20–40	Inactive	0.25 mg
Lorazepam	Intermediate (PO) rapid (IV)	10–20	Inactive	1 mg
Oxazepam	Slow	10–20	Inactive	15 mg
Temazepam	Slow	10–20	Inactive	30 mg
Long Acting				
Chlordiazepoxide	Intermediate (PO)	5–30	3–100	10 mg
Diazepam	Rapid (PO, IV)	20–50	3–100	5 mg
Flurazepam	Rapid	Inactive	50–100	30 mg

Source: Bosse GM. Benzodiazepines. In: Tintinalli JE, Kelen GD, Stapczynski JS, eds. Emergency Medicine. New York: McGraw-Hill; 2004:1005–57.

COMPREHENSION QUESTIONS

20.1 An 18-year-old male is having difficulty sleeping because of the death of his grandfather. He is given a benzodiazepine that does which of the following?

A. Binds to serotonin 5-HT_1 receptors
B. Binds to $GABA_A$ receptors
C. Is an antagonist at α-adrenoceptors
D. Is an antagonist at dopamine D_2 receptors

20.2 A 22-year-old woman is diagnosed with a generalized anxiety disorder. Which of the following is a contraindication for the use of a benzodiazepine to treat this patient?

A. Cigarette smoking
B. Seizure disorder
C. Diabetes mellitus
D. Sleep apnea

20.3 A 35-year-old man complains of seeing giant spiders in the hospital room. He is tremulous and agitated, is hypertensive, and admits to heavy alcohol use at home. Which of the following actions of the benzodiazepines is the main rationale for their use to manage this patient?

A. Vasodilation
B. Hypnosis
C. Cross-tolerance with alcohol
D. Elevation of mood

20.4 An 18-year-old man is brought into the emergency department with a seizure that has lasted 15 minutes without resolution. After administering oxygen, which pharmacologic agent is most appropriate to arrest the seizure?

A. Lidocaine
B. Lorazepam
C. Chlordiazepoxide
D. Triazolam

ANSWERS

20.1 **B.** Benzodiazepines bind to $GABA_A$ receptors to increase chloride influx and to decrease stimulation of neurons by excitatory neurotransmitters.

20.2 **D.** Sleep apnea is a condition of relaxed soft tissue of the posterior pharynx, which occludes the airway during sleep. Family members usually note loud snoring and episodes of apnea of affected individuals. Sedatives, alcohol, and muscle relaxants are contraindicated in these patients, because severe apnea and death may ensue.

20.3 **C.** Because there is cross-tolerance between them (they both interact with the $GABA_A$ receptor), a long-acting benzodiazepine can be used to ameliorate the symptoms associated with alcohol withdrawal.

20.4 **B.** A short-acting benzodiazepine such as lorazepam is usually the best choice in the acute setting to arrest status epilepticus. Triazolam is used as a hypnotic agent.

PHARMACOLOGY PEARLS

- Benzodiazepines bind to the $GABA_A$ receptor complex, increasing chloride influx, rendering the cell less excitable. Because alcohol and barbiturates also bind to the $GABA_A$ receptor complex, there is cross-tolerance among these agents.
- Benzodiazepine overdose causes sedation, hypotension, and respiratory depression. Alcohol and barbiturates can potentiate these effects and also lead to coma and death.
- Acute benzodiazepine withdrawal can cause tremor, anxiety, tachycardia, hallucinations, and life-threatening seizures.
- Flumazenil is a competitive inhibitor of benzodiazepines and will quickly reverse its effects, sometimes inducing withdrawal symptoms.

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CASE 21

A 30-year-old woman presents to the office for treatment of an ingrown toenail. For the past 3 weeks she has had progressively worsening redness, swelling, and pain from the area around the right great toenail. On examination you find that the distal, medial corner of the right great toenail is ingrowing. The skin on the medial border of the nail is red and tender. There is a visible purulent drainage as well. You place her on a 1-week course of oral cephalexin and have her return to the office. On follow-up, the redness is markedly improved, and there is no further drainage. You surgically correct the ingrown toenail after achieving local anesthesia with 2 percent lidocaine injected to infiltrate the digital nerves.

- What is the mechanism of action of lidocaine as an anesthetic agent?
- Why does the treatment of infection increase the effectiveness of the local anesthetic?

ANSWERS TO CASE 21:
Local Anesthetics

Summary: A 30-year-old woman with an infected, ingrown toenail receives lidocaine as a local anesthetic.

- **Mechanism of action of lidocaine:** Binds to voltage-gated sodium channels, which are located primarily in the axon hillock, thus inhibiting the initiation of action potentials and blocking nerve transduction.
- **Reason for treating infection prior to use of local anesthetic:** Infection and inflammation lower tissue pH, reducing the diffusion of the agent into the nerve, thus reducing its effectiveness.

CLINICAL CORRELATION

Local anesthetics produce a transient loss of sensation in a defined region of the body without producing a loss of consciousness. They may be used topically, for infiltration, for field block, for intravenous regional block, for nerve block, and for spinal and epidural anesthesia. Lidocaine and related local anesthetics work by inactivating Na^+ channels on axonal membranes, raising the threshold for axonal excitation. Nerves that carry pain and temperature signals tend to lack myelination, rendering them more susceptible to the effects of local agents compared to nerves that perform proprioception or motor functions. Some local anesthetics are effective topically, but most require injection into tissue, around nerves, or into the subarachnoid or epidural space.

Most local anesthetics are weak bases, and therefore, at physiologic pH, a greater proportion will reside in the cationic charged form, which is thought to be the active form. However, it is the uncharged form that is important for penetration of local anesthetics into biological membranes. When tissue pH is lowered by infection or inflammation, more of the anesthetic is in the cationic form. This reduces its diffusion into the nerve and can reduce its anesthetic effect. Lidocaine and related anesthetics are vasodilators.

Local anesthetics are frequently coadministered with dilute solutions of epinephrine, which produces vasoconstriction. This slows the absorption of the anesthetic, which prolongs its effect and lowers the risk of systemic toxicity. Epinephrine administration is contraindicated in areas supplied by end arteries, such as the digits, the tip of the nose, and the penis, as vasoconstriction of end arteries may result in tissue ischemia and necrosis.

APPROACH TO:

Pharmacology of Local Anesthetics

OBJECTIVES

1. List the drugs used for local anesthesia.
2. Describe the metabolism, adverse effects, and toxicities of local anesthetics.

DEFINITIONS

Nystagmus: Rapid, involuntary movement of the eye.

Purulent: Containing or consisting of pus.

Propioception: Receipt of stimuli originating from internal organs.

DISCUSSION

Class

Depending on their structure, local anesthetics are classified as either **esters** or **amides** (Table 21–1). The choice of local anesthetic depends on the specific procedure and is usually based on the **desired duration of action,** which may be **short** (procaine and chloroprocaine), **intermediate** (mepivacaine, lidocaine, prilocaine), or **long** (bupivacaine, etidocaine, ropivacaine, tetracaine). **Cocaine,** which has its own inherent vasoconstrictor properties, is used primarily for topical local anesthesia of the nose and throat.

Application of **very high levels of local anesthetics,** particularly lidocaine, may result in a **neurotoxicity** referred to as transient radicular irritation. High systemic local anesthetic levels, usually from **accidental intravascular injection, may result in central nervous system (CNS) effects** that may include symptoms ranging from light-headedness and visual disturbances to **nystagmus** and **muscle twitching** to tonic-clonic **seizures, respiratory depression, and death.** Most local anesthetics produce hypotension and decreased cardiac conduction, and in rare instances cardiovascular collapse. In contrast, cocaine overdose produces vasoconstriction and hypertension and may result in cardiac arrhythmias. Bupivacaine, which binds with a greater duration to the Na^+ channels, is more cardiotoxic than other local

Table 21–1 • LOCAL ANESTETHICS (ROUTE)

Esters	Amides
Cocaine*	Bupivacaine†
Benzocaine*	Lidocaine†
Procaine†	Mepivacaine†
Tetracaine†,*	Prilocaine†
Ropivacaine†	

* topical; † parenteral.

anesthetics. **Ester-type local anesthetics** are metabolized to para-aminobenzoic acid derivatives and may result in **allergic reactions** in some patients.

Structure

Local anesthetics generally consist of some ionizable group connected through either an ester or an amide to a lipophilic group.

Administration

Depending on the drug, local anesthetics may be administered by the parenteral route and topically. The extent of systemic absorption of injected local anesthetics from the site of administration, and therefore the duration of their action, is modified by a number of factors. Vasoconstrictor agents like epinephrine are used to decrease local blood flow and thus extend the duration of anesthetic action, and reduce the toxicity, of such local anesthetics as lidocaine, procaine, and mepivacaine. In spinal analgesia, clonidine can also be used concomitantly with local anesthetics to enhance the activation by epinephrine of α_2-adrenoceptors, which reduces sensory nerve firing by inhibition of the release of substance P. Bupivicaine has a prolonged duration of action and can be used for longer procedures or when epinephrine is not tolerated.

Pharmacokinetics

Ester-type local anesthetics are metabolized rapidly by **nonspecific plasma cholinesterases** and, generally, have **shorter half-lives** than amide-type local anesthetics.

Amide-type local anesthetics are metabolized at various rates by **hepatic microsomal enzymes.** In severe liver disease, toxicity is more likely. Likewise, metabolism may be slowed when amide-type local anesthetics are used with other drugs metabolized by the same enzymes.

COMPREHENSION QUESTIONS

21.1 Local anesthetic action is a result of blockade of the movement of which of the following ion channels?

A. Calcium
B. Chloride
C. Potassium
D. Sodium

21.2 A 25-year-old woman is being treated for a laceration to the forearm. Local anesthesia is used prior to suturing. An allergic reaction is most likely to occur with which of the following local anesthetics?

A. Bupivacaine
B. Lidocaine
C. Mepivacaine
D. Procaine

21.3 Which of the following agents is often combined with local anesthetics to prevent its systemic distribution from the site of injection?

A. Acetylcholine
B. Dopamine
C. Epinephrine
D. γ-Aminobutyric acid (GABA)

ANSWERS

21.1 **D.** Local anesthetic action is a result of prevention of sodium movement caused by blockade of the inactivated state of neuronal sodium channels.

21.2 **D.** An allergic reaction is most likely to occur with ester-type local anesthetics like procaine because of the metabolic formation of the allergen, para-aminobenzoic acid.

21.3 **C.** Local anesthetics are often combined with the vasoconstrictor epinephrine to prevent their distribution from the site of injection and thus extend their duration of action and reduce their systemic toxicity.

PHARMACOLOGY PEARLS

- Use of a carbon dioxide-saturated local anesthetic solution ("carbonation") to increase acidity can accelerate onset of anesthetic action.
- Ester-type local anesthetics are metabolized rapidly by nonspecific plasma cholinesterases and generally have shorter half-lives than amide-type local anesthetics.
- High systemic local anesthetic levels, usually from accidental intravascular injection, may result in CNS effects, tonic-clonic seizures, respiratory depression, and death.

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CASE 22

A 35-year-old man is in the surgical holding area being evaluated prior to a scheduled hernia repair. He asks the anesthesiologist about the type of "anesthetic gas" to be used, because he recalls that his mother developed severe liver problems from general anesthesia for a hysterectomy performed 2 years previously. The patient asks whether nitrous oxide might be used, because he has heard that it was a safe agent. To allay the patient's anxiety, the anesthesiologist proposes spinal anesthetic for the surgery.

- What was the probable general anesthetic agent used for the patient's mother?
- What is the disadvantage of nitrous oxide as an inhalation anesthetic agent?

ANSWERS TO CASE 22:
Inhalation Anesthetic Agents

Summary: A 35-year-old man is in the surgical holding area being evaluated prior to a scheduled hernia repair. The patients' mother developed severe liver problems from general anesthesia. The patient asks whether nitrous oxide might be used.

- **Probable inhalation anesthetic agent used for the patient's mother:** A halogenated agent, such as halothane.
- **Disadvantage of nitrous oxide as an inhalation anesthetic agent:** Lack of anesthetic potency requires large amounts to be used as a single agent, associated with postoperative nausea and vomiting.

CLINICAL CORRELATION

Patients such as the one described in the case are often nervous about "being put to sleep" because of fear about not having sufficient anesthesia and feeling pain, or about "never waking up." However, this is highly unlikely because the expertise in the field of anesthesia and the knowledge of the anesthetic agents is better today than ever before.

This patient relates a story of how his mother developed severe liver problems as a result of a general anesthetic agent. Halothane-related mild type I hepatotoxicity is benign, self-limiting, and relatively common, affecting up to 25 percent of individuals, and is characterized by mild, transient increases in serum transaminase and by altered postoperative drug metabolism. However, halothane-related type II hepatotoxicity is associated with massive centrilobular liver cell necrosis often leading to fulminant liver failure. The patient clinically has fever, jaundice, and a grossly elevated serum transaminase level that is probably immune mediated. Approximately 20 percent of halothane is oxidatively metabolized compared to only 2 percent of enflurane and 0.2 percent of isoflurane. Halothane-induced hepatotoxicity may result from the anaerobic formation of reductive reactive intermediates during halothane metabolism, including trifluoroacetic acid (TFA), that cause direct liver damage or initiate an immune response in genetically predisposed individuals. The occurrence of type II hepatotoxicity after enflurane or isoflurane administration is extremely rare, approximately 1 in 35,000 individuals.

APPROACH TO:
Pharmacology of Inhalation Anesthetic Agents

OBJECTIVES

1. List the characteristics of the ideal general anesthetic agent.
2. Describe the pharmacokinetic parameters of inhalation anesthetics that influence the onset of and recovery from anesthesia.

3. List the advantages and disadvantages of the commonly used inhalation anesthetic agents.
4. List the commonly used intravenously administered anesthetic agents and adjunct agents used in a "balanced anesthesia."

DEFINITIONS

Minimum alveolar concentration (MAC): Anesthetic dose of an inhalation anesthetic agent at 1 atmosphere, expressed in terms of alveolar tension (mm Hg), which produces immobility in 50 percent of individuals exposed to a noxious stimulus, such as a standardized skin incision.

Blood:gas partition coefficient: The solubility of an inhalation anesthetic in blood relative to air at 37°C (98.6°F).

Second gas effect: The rate of rise of alveolar tension and inflow of an inhalation anesthetic gas can be increased in the presence of high concentrations of another anesthetic gas, usually nitrous oxide.

DISCUSSION

Class

Inhalation anesthetics, as the name implies, are administered via the pulmonary route, often by assisted ventilation. The **ideal anesthetic agent** should be able to induce **unconsciousness, analgesia, amnesia, skeletal muscle relaxation,** and **inhibition of autonomic and sensory reflexes.** However, in practice, a combination of drugs ("balanced anesthesia"), including anesthetic agents that are administered intravenously, is used to provide a more satisfactory anesthesia than is possible with any one anesthetic agent alone, and to minimize their individual adverse effects (Table 22–1).

The **MAC** of an inhalation anesthetic that is necessary to achieve effective anesthetic concentrations is usually expressed as the mole fraction of the gas. Mole fraction equals partial pressure of anesthetic agent as percentage of total gas pressure (760 mm Hg). For example,

$$\text{Halothane's MAC} = 5.7 \text{ mm Hg}/760 \text{ mm Hg} \times 100 = 0.75\%$$

MAC is an indicator of anesthetic potency; the **lower the MAC,** the **more potent** is the agent (Table 22–2). It is used only as a guide. For example, the anesthesiologist might use either multiples of an inhalation anesthetic agent's MAC or a fraction of an inhalation anesthetic agent's MAC to achieve clinical anesthesia depending on whether or not the agent is used alone (rare for volatile anesthetics), in combination, or with intravenously administered anesthetic agents or preanesthetic agents (Table 22–3).

The blood:gas partition coefficient is a measure of the solubility of the gas in blood (Table 22–2). Anesthetic agents must become saturated in blood prior to uptake in the brain, the primary target for anesthetic action. A high partition coefficient indicates that the anesthetic requires a higher concentration for blood

Table 22–1 • ADVANTAGES AND ADVERSE EFFECTS OF INHALATION ANESTHETIC AGENTS

Anesthetic Agents*	Advantages	Adverse Effects
Nitrous oxide (N_2O; for minor surgery, used with volatile or intravenous anesthetics)	Odorless rapid induction, minimal cardiovascular effects	Postoperative nausea and vomiting, synergistic respiratory depression with other drugs (opioids, benzodiazepines)
Desflurane (used to maintain anesthesia after induction with another agent)	Very rapid recovery, cardiac output maintained, heart is not sensitized to catecholamines, minimal metabolism to toxic products	Objectionable odor, irritates respiratory tract, decreases blood pressure, tachycardia
Sevoflurane	Pleasant odor, very rapid induction and recovery	Decreases cardiac output, decreases blood pressure, reflex tachycardia
Enflurane	Pleasant odor	Decreases cardiac output, marked decrease in blood pressure, tachycardia, sensitized heart to catecholamine-induced arrhythmias, depresses neuromuscular transmission, can induce seizures
Isoflurane	Rapid induction and recovery, cardiac output maintained, heart is not sensitized to catecholamines, preserves tissue perfusion, very little metabolism to toxic products	Objectionable odor, decreases blood pressure, transient tachycardia, depresses neuromuscular transmission
Halothane† (used primarily in pediatrics)	Pleasant odor, rapid induction, and recovery	Depresses respiratory function, decreases cardiac output, decreases blood pressure, sensitizes heart to catecholamine-induced arrhythmias, increases cerebral blood flow with increased intracranial pressure, toxic metabolites that may cause hepatotoxicity

*Although available for use, the inhalation anesthetic methoxyflurane is considered obsolete because of potential renal and nephrotoxicity.
†Use is declining.

saturation and indicates that a larger amount of the drug must be used to achieve the anesthetic effect.

Most halogenated inhaled anesthetic agents reduce peripheral vascular resistance with the possibility of reflex tachycardia. Halothane is a notable exception in that it has both vascular constrictor and relaxation activity and blocks reflex sympathetic stimulation of the heart. However, it does sensitize the heart to catecholamine-induced arrhythmias.

Table 22–2 • MAC VALUES (%)* AND BLOOD:GAS PARTITION COEFFICIENTS OF SELECTED INHALATION ANESTHETIC AGENTS

Anesthetic Agent	Mac	Partition Coefficient
Nitrous oxide	>100.00†	0.47
Desflurane	6.00	0.42
Sevoflurane	2.00	0.69
Enflurane	1.70	1.80
Isoflurane	1.40	1.40
Halothane	0.75	2.30

*Expressed as a percentage of lung gases at 1 atmosphere.
†MAC values greater than 100 indicate that hyperbaric conditions are necessary to produce anesthesia.
MAC = minimum alveolar concentration.

Malignant hyperthermia is a **life-threatening, autosomal-dominant disorder** that develops during or after general anesthesia with volatile anesthetics and muscle relaxants (eg, succinylcholine). Its incidence is 1:10,000. Symptoms include a rapidly occurring hypermetabolic state of **tachycardia, hypertension, severe muscle rigidity, hyperthermia, acidosis, and hyperkalemia.** The biochemical basis of malignant hyperthermia is compromised regulation of calcium flux with increased intracellular concentrations of calcium in skeletal muscle. Treatment includes dantrolene, which prevents release of calcium from the sarcoplasmic reticulum, and supportive measures such as procedures to reduce body temperature and restore electrolyte balance.

Structure

With the exception of nitrous oxide, the major inhalation anesthetic agents in current use today are **halogenated hydrocarbons.** They are either gaseous (nitric oxide) with boiling points below room temperature or volatile liquids that at room temperature vaporize to the extent necessary to achieve anesthetic concentrations.

Table 22–3 • SELECTED INTRAVENOUS ANESTHETIC AGENTS AND PREANESTHETIC AGENTS

Anesthetic Agents	Preanesthetic Agents
Barbiturates (eg, thiopental)	Sedative-hypnotics
Benzodiazepines (eg, diazepam, midazolam, lorazepam)	Opioids Muscle relaxants
Opioids (eg, fentanyl, sufentanil, alfentanil, remifentanil)	Anticholinergic agents Local anesthetics
Ketamine	
Propofol	
Etomidate	

Mechanism of Action

The mechanism of action of inhalation anesthetics is not well understood. Older theories based on the lipid solubility of these agents suggested that the effects were nonspecific interactions with lipids in cell membranes. Current theories suggest that anesthetics directly interact with proteins at hydrophobic sites on ligand-gated ion channels at neural synapses to inhibit the activity of excitatory receptors (eg, *N*-methyl-D-aspartic acid [NMDA], nicotinic, serotonin 5-HT_3) or potentiate the activity of inhibitory receptors (eg, $GABA_A$, glycine).

Pharmacokinetics

The concentration of an inhaled gas in the brain sufficient to achieve anesthesia depends on a number of factors, including the anesthetic agent's concentration in the inspired air, its **solubility** in blood relative to air, the **arteriovenous concentration gradient,** as well as **pulmonary blood flow and pulmonary ventilation rate.**

The concentration (as a percentage) of an inhaled anesthetic in the inspired air directly affects the rate of induction of anesthesia by influencing the rate of transfer of the agent into blood. In clinical practice, an inhaled anesthetic may be administered initially at a relatively high concentration to speed the rate of induction, following which the concentration in the inspired air would be reduced to a level that maintains the anesthetic state.

The solubility of an inhalation anesthetic in blood relative to air at 37°C (98.6°F), as described by its **blood:gas partition coefficient** (see Table 22–2), is an important factor in determining the rate of rise of their arterial tension in the arterial blood, which influences directly the rate of equilibration with the brain and rate of onset of action. For anesthetic agents with low blood solubility, the partial pressure, and therefore the arterial tension, rises relatively quickly. The partial pressure and arterial tension rise more slowly with anesthetic agents of moderate to high solubility.

The greater the difference in the arterial and venous anesthetic concentrations, the more time it will take for an inhaled anesthetic agent to equilibrate with brain tissue and to induce surgical anesthesia. The difference in the arterial and venous anesthetic concentrations is a reflection of the uptake of an anesthetic agent by the tissues, particularly muscle, kidney, liver, and splanchnic bed (which in turn is a reflection of, among other factors, blood flow, and tissue solubility relative to blood).

Pulmonary blood flow also affects the rate of induction of anesthesia. Although counterintuitive, the higher the blood flow (and the higher the cardiac output), the slower the rate of rise of arterial tension, an effect that is most notable for inhaled anesthetics of moderate to high blood solubility. The opposite occurs with a decrease in blood flow, as might occur during shock.

An increase in **pulmonary ventilation rate** (ie, minute ventilation), for example, by mechanical hyperventilation, increases anesthetic gas tension and the speed of induction, most notably for inhalation anesthetic agents with moderate to high blood solubility. Depression of unassisted respiration will have the opposite effect.

The **second gas effect** can also be taken advantage of to increase the rate of rise of alveolar tension of an inhalation anesthetic gas. Typically this occurs when nitrous oxide is used in combination with a volatile anesthetic (halothane or isoflurane).

Alveolar diffusion of nitrous oxide effectively increases the concentration of the second anesthetic, thereby increasing the rise in alveolar tension of the second agent.

Following termination of its administration, recovery from anesthesia depends on the rate of elimination of an anesthetic agent from the brain, which can be influenced by pulmonary blood flow and pulmonary ventilation, and by the tissue solubility and the blood solubility of the anesthetic agent. Clearance by the lungs is the major route of elimination of inhalation anesthetic agents, with perhaps metabolism playing a contributing role for halothane.

COMPREHENSION QUESTIONS

22.1 Which of the following is most important to quickly achieve a partial pressure of an inhalation anesthetic agent of high blood solubility that is sufficient to induce anesthesia?

A. A decrease in pulmonary ventilation rate
B. Coadministration of dantrolene
C. Low blood and tissue solubility
D. Low MAC

22.2 An inhalation agent with a low (1.7) MAC has which of the following?

A. A rapid onset of action
B. A low blood:gas partition coefficient
C. A low oil:gas partition coefficient
D. A high potency

22.3 A 34-year-old woman is undergoing general anesthesia for a cholecystectomy. After the completion of the case, the anesthesiologist turns off the gas and notes that the patient is recovering from the anesthetic agent very quickly. What are likely properties of this inhalation anesthetic?

A. Associated with decreased pulmonary circulation
B. Associated with an unpleasant odor
C. High MAC
D. High solubility

22.4 Treatment of malignant hyperthermia is achieved with the administration of an agent that has this mechanism of action:

A. Inhibition of calcium release from the sarcoplasmic reticulum
B. Reversal of muscle relaxation achieved with succinylcholine
C. Inhibition of Cox-2
D. Alteration of cellular pH

ANSWERS

22.1 **C.** The alveolar partial pressure of an inhalation anesthetic with low blood and tissue solubility will rise quickly. Under these conditions, blood and brain will equilibrate, and anesthesia will be induced, rather quickly. An inhalation anesthetic with a low MAC will equilibrate with brain tissue rather slowly. An increase, not decrease, in pulmonary ventilation rate will increase anesthetic gas tension and the speed of induction, particularly for inhalation anesthetic agents with moderate to high blood solubility. Dantrolene is not an anesthetic agent. It is used to counter the effects of malignant hyperthermia.

22.2 **D.** An agent with a low MAC is highly potent, has a high oil:gas partition coefficient and high blood:gas partition coefficient, and usually has a slow onset of action.

22.3 **B.** Agents that have a rapid onset of action and rapid recovery have a low solubility. One such agent is desflurane, which has an unpleasant odor.

22.4 **A.** Dantrolene acts on intracellular calcium channels to prevent the release of calcium from intracellular stores, which has the effect of reducing cardiac muscle contraction.

PHARMACOLOGY PEARLS

- Modern-day inhalation anesthetic agents cause a rapid progression through the classical Guedel stages of anesthesia (analgesia, loss of consciousness, surgical anesthesia, and respiratory and cardiovascular depression).
- Although independent of gender and weight, MAC may be decreased (increased potency) with age, pregnancy hypothermia, and hypotension.
- MAC may increase (decreased potency) with CNS stimulants.

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CASE 23

A 50-year-old salesman was admitted to the hospital with acute appendicitis. He has no significant medical history, takes no medications, does not smoke cigarettes, and has an alcoholic beverage "once in a while with the boys." He underwent an uncomplicated appendectomy. On the second hospital day, you find him to be quite agitated and sweaty. His temperature, heart rate, and blood pressure are elevated. A short time later he has a grand mal seizure. You suspect that he is having withdrawal symptoms from chronic alcohol abuse and give IV lorazepam for immediate control of the seizures and plan to start him on oral chlordiazepoxide when he is more stable.

- What are the acute pharmacologic effects of ethanol?
- What are the chronic pharmacologic effects of ethanol?
- How is alcohol metabolized?
- What is the pharmacologic basis for using benzodiazepines to manage alcohol withdrawal?

ANSWERS TO CASE 23:
Drugs of Abuse

Summary: A 50-year-old man is displaying symptoms and signs of acute alcohol withdrawal.

- **Symptoms of acute ethanol toxicity:** Disinhibited behavior and judgment, slurred speech, impaired motor function, depressed and impaired mental function, respiratory depression, cutaneous vasodilation, diuresis, gastrointestinal side effects, and impaired myocardial contractility.
- **Symptoms of chronic ethanol toxicity:** Alcoholic fatty liver, alcoholic hepatitis, cirrhosis, liver failure, peripheral neuropathy, alcohol amnesic syndrome, pancreatitis, gastritis, fetal alcohol syndrome, nutritional deficiencies, cardiomyopathy, cerebellar degeneration.
- **Metabolism of alcohol:** Oxidized primarily in the liver but also in the stomach and other organs to acetaldehyde by the cytosolic enzyme alcohol dehydrogenase and by hepatic microsomal enzymes; acetaldehyde is oxidized to acetate by hepatic mitochondrial aldehyde dehydrogenase.
- **Benzodiazepines in alcohol withdrawal:** Both alcohol and the benzodiazepines enhance the effect of γ-aminobutyric acid (GABA) on $GABA_A$ receptors, resulting in decreased overall brain excitability. This cross-reactivity explains why relatively long-acting benzodiazepines (eg, lorazepam, chlordiazepoxide) can be substituted for alcohol in a detoxification program.

CLINICAL CORRELATION

Ethanol is the most widely used CNS depressant. It is rapidly absorbed from the stomach and small intestine and distributed in total body water. Its exact mechanism of action is not known, but may be related to its generally disruptive effects on cell membrane protein functions throughout the body, including effects on signaling pathways in the CNS. At low doses it is oxidized by cytoplasmic alcohol dehydrogenase. At higher doses it is also oxidized by liver microsomal enzymes, which may be induced by chronic use. These enzymes are rapidly saturated by the concentrations of alcohol achieved by even one or two alcoholic drinks so that its rate of metabolism becomes independent of plasma concentration. Tolerance to the intoxicating effects of alcohol can develop with chronic use. Genetic variations in aldehyde dehydrogenase occur such that certain individuals display impaired ability to metabolize alcohol. The acetaldehyde metabolite accumulates in these individuals causing demonstrate a characteristic flushing of the skin upon drinking alcohol and increasing the likelihood of acute alcohol intoxication.

Cross-tolerance with barbiturates and benzodiazepines may also develop. Because of this cross-tolerance effect, benzodiazepines are the most commonly used agents for the treatment of alcohol withdrawal, a potentially life-threatening syndrome commonly seen 2–3 days after the abrupt cessation of alcohol use by a chronic

abuser. A long-acting benzodiazepine can be taken, and gradually tapered, to mitigate this effect. Disulfiram is also used on occasion to manage alcoholism. It is a drug that inhibits aldehyde dehydrogenase that in the presence of alcohol causes an accumulation of acetaldehyde, which results in a highly aversive reaction consisting of flushing, severe headache, nausea and vomiting, and confusion. Naltrexone, an opioid antagonist, is yet another drug used to manage alcoholism.

APPROACH TO:
Pharmacology of Drugs of Abuse

OBJECTIVES

1. Define drug abuse, drug tolerance, drug dependence, and drug addiction.
2. List the common drugs of abuse and their properties.
3. List the adverse effects of the common drugs of abuse.
4. Describe pharmacological treatment of alcohol and nicotine addiction.

DEFINITIONS

Drug abuse: Nonmedical use of a drug taken to alter consciousness or to change body image that is often regarded as unacceptable by society. Not to be confused with drug misuse.

Drug tolerance: Decreased response to a drug with its continued administration that can be overcome by increasing the dose. A cellular tolerance develops to certain drugs of abuse that act on the CNS because of a poorly understood biochemical or homeostatic adaptation of neurons to the continued presence of the drug. Also, in addition to a cellular tolerance, a metabolic tolerance can develop to the effects of some drugs because they increase the synthesis of enzymes responsible for their own metabolism (alcohol, barbiturates).

Drug dependence: Continued need of the user to take a drug. Psychologic dependence is the compulsive behavior of a user to continue to use a drug, no matter the personal or medical consequences. Inability to obtain the drug activates a "craving" that is very discomforting. Physical or physiologic dependence is a consequence of drug abstinence after chronic drug use that results in a constellation of signs and symptoms that are often opposite to the initial effects of the drug and to those sought by the user. Psychologic dependence generally precedes physical dependence but, depending on the drug, does not necessarily lead to it. The development of physical dependence, the degree of which varies considerably for different drugs of abuse, is always associated with the development of tolerance, although the exact relationship is unclear.

Drug addiction: A poorly defined, imprecise term with little clinical significance that indicates the presence of psychologic and physical dependence.

DISCUSSION

Class

In addition to alcohol, the major drugs of abuse are nicotine, marijuana (Δ9-tetrahydrocannabinol), and the CNS stimulants, notably cocaine and amphetamine and its derivatives (Table 23–1).

Three agents are approved for the pharmacological management of alcohol abuse. **Disulfiram** inhibits aldehyde dehydrogenase to increase the accumulation of acetaldehyde. Exposure to alcohol in the presence of this drug causes flushing, headache, palpitations, nausea/vomiting, and decreased blood pressure. These adverse reactions can discourage impulsive alcohol consumption. **Naltrexone** blocks the μ-opioid receptor to decrease alcohol cravings. It may be most effective in those with a genetic predisposition to alcohol dependence. Its use is limited by potential liver toxicity. A depot preparation of this drug is available. **Acamprosate** modulates glutamate neurotransmission by acting at central metabotropic glutamate receptors. Although this drug is generally well tolerated, its effectiveness remains equivocal. It can be combined with naltrexone.

Nicotine replacement for smoking cessation is available in patch, gum, inhaler, lozenge, and nasal spray. Patch provides a continuous supply of nicotine, whereas the other routes of administration provide the opportunity for the patient to respond to cravings. Patch, gum, and lozenges are available over the counter, whereas the inhaler and nasal spray require a prescription. Although nicotine is a vasoconstrictor, its use in smoking cessation is safe even in patients with cardiovascular disease. **Varenicline** is a partial agonist for nicotinic cholinoreceptor. Its partial agonist properties reduce nicotine withdrawal. By occupying the nicotinic cholinoreceptor, it prevents binding of nicotine to block the "reward" of smoking. **Bupropion** is an antidepressant that affects norepinephrine and dopamine systems. Its effectiveness in smoking cessation is independent of its antidepressant effects. Side effects include insomnia, agitation, and, rarely, seizures.

Table 23–1 • DRUGS OF ABUSE			
	Nicotine	**Marijuana**	**Cocaine/Amphetamine**
Route of administration	Smoking	Smoking	Smoking, oral IV
Mechanism of action	Mimics action of acetylcholine	Interacts with G-protein-coupled cannabinoid receptors among other actions	Cocaine binds the dopamine reuptake transporter. Amphetamine increases release of neuronal catecholamines, including dopamine
Pharmacologic effects	Stimulant and depressant actions on the CNS and cardiovascular system	Euphoria, uncontrollable laughter, introspection, loss of sense of time, sleepiness, loss of concentration	Euphoria, excitation, increased alertness, an orgasmic-like "rush"
Tolerance and dependence	Tolerance develops rapidly Strong psychologic dependence Withdrawal syndrome indicative of physical dependence	Arguably, some tolerance and very mild physical dependence	Rapid development of tolerance. Withdrawal syndrome characterized by increased appetite, depression, and exhaustion
Therapeutic uses	None	Nausea and vomiting of cancer. Appetite stimulation in AIDS (dronabinol)	Local anesthesia (cocaine). ADHD (methylphenidate). Narcolepsy (modafinil)
Adverse effects	Cancer, obstructive lung disease, cardiovascular disease	Bronchitis, increased pulse rate, reddening of conjunctiva Effects on sperm, libido alteration, decreased testicular size, association w. cancer, paranoa, lung disease due to increased tar content, and lack of filter compared to cigarettes	Paranoid schizophrenia. Amphetamine-specific necrotizing arteritis. Cocaine-related arrhythmias, seizures, respiratory depression, hypertension, stroke, increased fetal mortality, and abnormalities
Treatment of abuse	Nicotine gum and transdermal patch	Behavioral modification	Antipsychotic agents. Antidepressant agents

COMPREHENSION QUESTIONS

23.1 Alcohol is oxidized by which of the following enzymes?

A. Acetate oxidase
B. Alcohol dehydrogenase
C. Decarboxylase
D. Monoamine oxidase

23.2 Which of the following is the most common adverse effect resulting from chronic ethanol abuse?

A. Cirrhosis
B. Cutaneous vasodilation
C. Disinhibited judgment
D. Respiratory depression

23.3 Which of the following is a drug of abuse that blocks the dopamine uptake transporter?

A. Alcohol
B. Cocaine
C. Marijuana
D. Nicotine

ANSWERS

23.1 **B.** Alcohol is oxidized in the liver, stomach, and other organs to acetaldehyde by the cytosolic enzyme ADH and the hepatic microsomal enzymes. Acetaldehyde is oxidized to acetate by mitochondrial hepatic aldehyde dehydrogenase.

23.2 **A.** Liver cirrhosis is an effect of chronic alcohol use. Disinhibited judgment, respiratory depression, and cutaneous vasodilation are acute effects of alcohol.

23.3 **B.** Cocaine is a drug of abuse that binds the dopamine reuptake transporter. Ethanol may nonspecifically disrupt cell membrane protein functions. Marijuana interacts with G-protein-coupled cannabinoid receptors. Nicotine mimics the action of acetylcholine.

PHARMACOLOGY PEARLS

- Alcohol is the most widely used drug of abuse.
- Delirium Tremens, a syndrome associated with the abrupt discontinuation of alcohol in a chronic abuser, carries a high mortality rate if not promptly identified and treated.
- Withdrawal from other drugs of abuse may cause unpleasant symptoms for the patient, but is rarely life threatening.
- In all hypotheses of addiction, increased concentrations of dopamine in the mesolimbic system is considered the neurochemical correlate of dependence and addiction.

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CASE 24

An 8-year-old girl is brought in by her mother for evaluation of allergies. Each year in the spring the child develops a runny nose; itchy, watery eyes; and sneezing. She has been treated in the past with diphenhydramine, but the child's teacher says that she is very drowsy during school. She has no other medical problems and is on no chronic medications. Her examination is unremarkable today. You diagnose her with seasonal allergic rhinitis and prescribe fexofenadine.

- What is the mechanism of action of antihistamine medications?
- What are the common side effects of antihistamine medications?
- What is the pharmacologic basis of switching to fexofenadine?

ANSWERS TO CASE 24:
Antihistamines

Summary: An 8-year-old girl with seasonal allergic rhinitis is switched to fexofenadine because of the sedation caused by diphenhydramine.

- **Mechanism of action of antihistamines:** Competitive antagonist of histamine receptors.
- **Common side effects:** Sedation, dizziness, nausea, constipation, diarrhea, loss of appetite, anticholinergic effects—dry mouth, dry eyes, blurred vision, urinary retention.
- **Rationale for switching to fexofenadine:** Less central nervous system (CNS) penetration and less sedating than earlier antihistamines.

CLINICAL CORRELATION

Histamine is found in many tissues throughout the body. Most histamine is stored in mast cells and basophils. Histamine is released primarily from mast cells via the process of degranulation. Degranulation occurs when immunoglobulin E (IgE) fixates to mast cells, and there is a subsequent exposure to a specific antigen. Complement activation may also induce degranulation. When released, histamine becomes bound to specific membrane-bound histamine receptors. The therapeutic uses of antihistamine medications primarily involve the H_1-and H_2-receptor subtypes. **H_1 receptors are located in the brain, heart, bronchi, gastrointestinal (GI) tract, and vascular smooth muscle.** Their activation increases phospholipase C activity, causing increases in diacylglycerol and intracellular calcium. Activation of H_1 receptors in the brain increases wakefulness. In blood vessels, activation causes vasodilation and increased permeability. H_1-receptor antagonists are competitive inhibitors at this receptor site. H_1-receptor antagonists are frequently used for the treatment of allergic rhinitis, urticaria, and hives. Some are used as prophylaxis for motion sickness and as sleep aids. Older, first-generation, antihistamines cross the blood-brain barrier, contributing to their potentially use-limiting side effect of sedation and can also have significant anticholinergic effects (dry mouth, dry eyes, blurred vision, urinary retention). They must be used with caution in the elderly and in combination with other sedating medications, because the effects can be additive. **Newer, second-generation antihistamines have significantly less penetration into the CNS and reduced anticholinergic activity.** This results in a lower incidence of sedation and fewer anticholinergic side effects. H_2-receptor activity is coupled to increased cyclic adenosine monophosphate (cAMP). **Activation of H_2 receptors in gastric parietal cells causes an increase in gastric acid production.** Medications that are competitive antagonists of H_2 receptors are used to reduce gastric acid secretion. These are used clinically in the management of peptic ulcer disease, gastroesophageal reflux disease, heartburn, and acid hypersecretory syndromes.

APPROACH TO:

Pharmacology of Histamine and Antihistamines

OBJECTIVES

1. Know the synthesis and mechanism of action of histamine.
2. Know the mechanism of action, uses, and adverse effects of antihistamine medications.
3. Understand the biology and pharmacology of the histamine receptors.

DEFINITIONS

Allergic rhinitis: An antigen-mediated allergic reaction that causes nasal congestion, sneezing, itchy eyes, and bronchoconstriction; also called hay fever.

DISCUSSION

Class

Histamine, β-aminoethylimidazole, is formed in many tissues by decarboxylation of the amino acid L-histidine by the enzyme histidine decarboxylase. Mast cells and basophils are the principal histamine-containing cells in most tissues. **Histamine is stored in vesicles in a complex with heparin** and is **released by either an immunologic trigger** or following a **mechanical or chemical stimulus.** Once released, **histamine produces a number of responses including local vasodilation, transudation of fluid through endothelial cells, and stimulation of nerve endings, producing pain and itching.** In the lung, histamine is a **bronchoconstrictor,** and this action is magnified in patients with asthma. Histamine has actions in the GI tract and causes **contraction of smooth muscle;** it is also a potent secretagogue for gastric acid secretion, pepsin, and intrinsic factor. In the brain, histamine acts as a **neurotransmitter.**

The actions of histamine are mediated by four distinct membrane receptors that are **coupled to G-proteins.** The H_1 receptor, located in smooth muscle cells, endothelium, and brain, is coupled to increased diacylglycerol and Ca^{2+} release. The H_2 receptor is located in gastric mucosa mast cells, immune cells, and brain, and is coupled to increased cAMP. There is no clinical pharmacology yet for H_3 (located in the brain and peripheral neurons) or H_4 (found on eosinophils and neutrophils) receptors, but both of these receptors are targets for therapeutic agents and are under intense investigation. Histamine itself has a variety of untoward effects and is useful only diagnostically to assess bronchial hyperreactivity.

Antihistamines Compounds that block the active state of histamine H_1 receptors have been used for years and are widely marketed both as prescription and over-the-counter medications. The current group of available drugs can be divided into **first-generation and second-generation agents.** In general, **first-generation agents can cross the blood-brain barrier,** and they have a number of effects in the brain,

Table 24–1 • CURRENTLY AVAILABLE ANTIHISTAMINES

Chemical Class	Drug	Antichol Activity	Comment
First-Generation Antihistamines			
Ethanolamines	Diphenhydramine Doxylamine Carbinoxamine	+++ +++ +++	I Sleeping aid
Ethylamine diamines	Pyrilamine Tripelennamine	+ +	
Piperazines	Cyclizine Meclizine Hydroxyzine	++ ++ ++	I Sedative
Alkylamines	Chlorpheniramine Brompheniramine	+ +	I
Phenothiazines	Promethazine Cyproheptadine	+++ +	I
Second-generation Antihistamines			
Piperidines	Fexofenadine Loratadine	Nil Nil	
Piperazines	Cetirizine Levocetirizine	Nil Nil	
Alkylamines	Acrivastine	Nil	
Phthalazinones	Azelastine	Nil	

I = available in an injection preparation; ANTICHOL = anticholinergic.

including sedation and reduction of nausea. Table 24–1 lists some currently used H_1 antagonists.

All of these drugs block the action of H_1 receptors, and they do not possess significant affinity for the H_2 receptor. However, many of the **first-generation agents** have **significant anticholinergic activity,** and this is responsible for a significant degree of their central effects. Second-generation agents are less lipid soluble and do not penetrate the blood-brain barrier and hence have many fewer central adverse effects.

The major use of H_1-receptor blockers is in the treatment of allergic reactions. Histamine is released by IgE-sensitized cells, especially mast cells, and antihistamines can reduce the rhinitis, conjunctivitis, sneezing, and urticaria associated with this reaction. They are most effective in acute allergic reactions with a relatively low antigen burden, and effectiveness diminishes in chronic disorders. Antihistamines are not effective as monotherapy for bronchial asthma. Antihistamines are marketed for treatment of the common cold, but they have very limited effectiveness in this application and their adverse effects (eg, sedation) outweigh their benefit. Some of the first-generation agents, especially dimenhydrinate, meclizine, cyclizine, and promethazine, are useful for the prophylaxis of motion sickness and vertigo. **Promethazine** is the most potent in this regard but has pronounced sedative activity that limits its usefulness. The sedating action of some antihistamines has been exploited in their use as sleeping aids.

Diphenhydramine is the most commonly used antihistamine in sleeping preparations. The **major adverse effect of the first-generation agents is sedation.** The **anticholinergic activity** produces atropine-like effects including dry mouth, urinary retention, and cough. Second-generation agents avoid these effects but do have adverse effects such as headache and back pain, and in the GI tract cause nausea, loss of appetite, and constipation or diarrhea. Of the presently available second-generation antihistamines, **cetirizine** causes the highest incidence of fatigue and somnolence (approximately 10%); loratadine and desloratadine appear to have the lowest incidence of this effect (approximately 1–3%). Desloratadine is unique among antihistamines in reducing nasal congestion.

These agents may produce cardiovascular adverse effects such as hypotension, bradycardia or tachycardia, and electrocardiograph (ECG) changes.

Administration

All of the agents listed in Table 24–1 are available for oral use, and some of the first-generation agents are available for parenteral use. Topical application of diphenhydramine is useful in the treatment of minor allergic dermatologic reactions. Azelastine is administered by nasal spray.

Pharmacokinetics

Following oral administration, the H_1 antagonists reach peak levels in about 2–3 hours and last 6–24 hours depending on the agent.

H_2-Receptor Antagonists

Histamine is a potent gastric acid secretagogue and this action is mediated by histamine H_2 receptors. Cimetidine, ranitidine, nizatidine, and famotidine are H_2-specific antagonists and are used to treat gastroesophageal reflux disease and peptic ulcers. Adverse effects include hypotension, headache, and diarrhea. Cimetidine inhibits many P450 enzymes and by this mechanism causes drug interactions.

COMPREHENSION QUESTIONS

24.1 The major use of second-generation histamine H_1-receptor blockers is the treatment of which of the following complaints?

A. Cough associated with influenza

B. Hay fever

C. Motion sickness

D. Sleeplessness

24.2 You see a 43-year-old man long-distance truck driver in the clinic who complains of serious allergic rhinitis. Which of the following would be the best antihistamine to prescribe?

A. Diphenhydramine
B. Fexofenadine
C. Meclizine
D. Promethazine

24.3 Which of the following statements is most accurate?

A. Antihistamine agents used for allergic rhinitis have antagonistic activity against both H_1 and H_2 receptors.
B. Antihistamine agents are generally useful in the treatment of asthma.
C. Antihistamines are the preferred agent in the treatment of acute anaphylaxis.
D. Second-generation antihistamines have fewer anticholinergic effects than first-generation antihistamines.

ANSWERS

24.1 **B.** First-generation agents that cause sedation have been used as sleeping aids, and some have antiemetic effects.

24.2 **B.** The other agents are sedating.

24.3 **D.** Second-generation antihistamines have less sedating and anticholinergic side effects than first-generation agents.

PHARMACOLOGY PEARLS

- Second-generation antihistamines do not penetrate the blood-brain barrier and have little sedative effect.
- Antihistamines are of little or no benefit in treating the common cold.

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CASE 25

A 40-year-old woman presents for evaluation of her chronic migraine headaches. She reports that approximately once a month she has a severe, unilateral headache associated with nausea and extreme photophobia. The headache will last for a full day if not treated. She has had success in reducing the severity of the headaches with opioid pain medications, but usually she is too nauseous to take them. When she is able to tolerate them, she will have to sleep for several hours afterward. She is missing about a day of work a month because of the headaches. She has no other significant medical history and takes no medications on a regular basis. Her examination today is normal. You decide to prescribe sumatriptan for her to try with her next migraine headache.

- Which receptor is the site of action of sumatriptan?
- What is the mechanism of action of sumatriptan?

ANSWERS TO CASE 25:

Serotonin Receptor Agonists and Antagonists

Summary: A 40-year-old woman with migraine headaches is treated with sumatriptan.

- **Receptor site of action of sumatriptan:** Serotonin 5-HT_{1D} and 5-HT_{1B} receptors.
- **Mechanism of action of sumatriptan:** Receptor activation inhibits the activity of adenylyl cyclase and decreases cAMP accumulation that results in contraction of arterial smooth muscle, especially in carotid and cranial circulation.

CLINICAL CORRELATION

Migraine headaches are common causes of severe symptoms among patients and a leading cause of absenteeism from work and school. Sumatriptan was the first of a class of serotonin (5-HT) agonist medications for the treatment of migraines. Multiple subtypes of 5-HT receptors have been identified. Sumatriptan specifically acts at the 5-HT_{1D} and 5-HT_{1B} receptor subtypes that are coupled to an inhibition of cAMP. Stimulation of these receptors results in vasoconstriction in the carotid circulation that may directly oppose the vasodilation and the release of vasodilating peptides thought to be involved in migraine.

At prejunctional sites, activation of these receptors results in decreased transmission of nociceptive signals in the trigeminal nerve. While being fairly specific for the carotid circulation, there can be activity at other vascular sites. Cerebrovascular, peripheral vascular, mesenteric arterial, or coronary artery diseases are all contraindications to its use. Vasospastic coronary disease is a contraindication as well.

APPROACH TO:

Pharmacology of Serotonin Receptor Agonists and Antagonists

OBJECTIVES

1. Describe the activity of the different classes of serotonin receptors.
2. List the agents that act as serotonin agonists and describe their mechanisms of action and uses.
3. List the agents that act as serotonin antagonists and describe their mechanisms of action and therapeutic uses.

DEFINITIONS

Partial agonist: A drug that at full receptor occupancy produces less of a response than a full agonist. Partial agonists can competitively inhibit the response to a full agonist, including the physiologic response to endogenously released hormones and neurotransmitters.

DISCUSSION

Class

Other than the **triptans** (almotriptan, eletriptan, frovatriptan, naratriptan, rizatriptan, sumatriptan, and zolmitriptan), which are the drugs of choice to treat acute, severe migraine headache, there are a few clinically important agents that are direct-acting serotonin receptor agonists. The **ergot alkaloids** (ergotamine [the prototype], dihydroergotamine, ergonovine, methylergonovine) act through the same mechanisms as the triptans and are **effective clinically during the prodrome of a migraine attack. Diarrhea, nausea and vomiting, and drowsiness** are their most common adverse effects. **Prolonged vasospasm** resulting from smooth muscle stimulation is a serious consequence of **overdose** that may result in **gangrene and amputation of arms, legs, or digits. Bowel infarction** has also been reported. They are **contraindicated** for patients with **obstructive vascular disease.**

Cisapride, a 5-HT_4 receptor agonist was voluntarily removed from the US market because of potential serious **cardiac arrhythmias;** however, it is still available for compassionate use. It promotes release of acetylcholine from the myenteric plexus and may be used to treat gastroesophageal reflux and motility disease.

The major clinical use of **selective serotonin receptor antagonists** is as first-line drugs for **treatment of nausea and vomiting,** resulting from **vagal stimulation that is associated with surgery and cancer chemotherapy.** These agents, the prototype being **ondansetron** (also granisetron, palonosetron, and dolasetron), act on 5-HT_3 receptors. Their most common adverse effects are **headache and constipation.** Dolasetron prolongs the QT interval and, therefore, should not be administered to patients with this condition or with other similarly acting drugs.

Alosetron is a 5-HT_3 receptor antagonist that is used to treat **IBS with diarrhea.** It is only approved for treatment of women because efficacy has not been documented for men. Its major adverse effects are constipation that may be severe and require discontinuation of therapy. **Ischemic colitis** (adverse incidence about 0.3%) may be **fatal** and therefore precludes the use of alosetron except for patients who have not responded to other therapies.

Mechanism of Action

The **ergot alkaloids** (dihydroergotamine, ergonovine, the prototype ergotamine, and methylergonovine) have **agonist and partial agonist activity at serotonin** (5-HT_{1D} receptors and 5-HT_{1A} receptors) that, like the triptans (see above), are responsible for their therapeutic action. Their antagonist and agonist and partial agonist activity at α-adrenergic receptors and dopamine receptors is responsible for some adverse actions. Cisapride and tegaserod activation of 5-HT_4 receptors on enteric neurons promotes release of acetylcholine that results in increased lower esophageal sphincter pressure. Ondansetron and other selective serotonin antagonists act

to inhibit nausea and vomiting through peripheral blockade of serotonin 5-HT_3 receptors on intestinal vagal afferent nerves, and through central blockade of serotonin 5-HT_3 receptors in the vomiting center and chemoreceptor trigger zone.

Alosetron and palonosetron are highly selective serotonin receptor 5-HT_3 antagonists that act peripherally on enteric afferent and cholinergic neurons to reduce intestinal activity and visceral afferent pain. It also acts centrally on the same receptors to inhibit afferent nerve activation of the CNS.

Administration

Sumatriptan may be administered orally, as a subcutaneous injection, or as a nasal spray, making it particularly valuable for migraine patients with nausea and vomiting as symptoms. Ergotamines are available for oral, sublingual rectal, parenteral, and inhaler administration.

Selective serotonin receptor antagonists can be administered orally or IV. They are most effective against nausea and vomiting when administered IV prior to the administration of chemotherapeutic agents.

Pharmacokinetics

Tegaserod is poorly absorbed and should be taken before meals. Severe hepatic or renal disease may significantly reduce its clearance. Ergotamine tartrate may be administered combined with caffeine, which facilitates its absorption.

COMPREHENSION QUESTIONS

25.1 A 35-year-old woman is diagnosed with migraine headaches. She is prescribed sumatriptan. Which of the following is an effect of sumatriptan?

A. Causes vasoconstriction in the carotid and cranial circulation
B. Increases transmission of nociceptive signals in the trigeminal nerve
C. Increases adenylyl cyclase activity
D. Is an antagonist at the 5-HT_{1D} receptor subtype

25.2 The major clinical use of ondansetron is which of the following?

A. Compassionate treatment of gastroesophageal reflux and motility disease
B. Major depression
C. Migraine headache
D. Nausea and vomiting that is associated with surgery and cancer chemotherapy

25.3 Prolonged vasospasm is a serious consequence of which of the following?

A. Alosetron
B. Cisapride
C. Ergotamine
D. Ondansetron

ANSWERS

25.1 **A.** Sumatriptan, a 5-HT_{1D} receptor agonist, inhibits the activity of adenylyl cyclase and decreases cAMP accumulation that results in contraction of arterial smooth muscle, especially in carotid and cranial circulation.

25.2 **D.** The major clinical use of ondansetron, a 5-HT_3 receptor antagonist, is for treatment of nausea and vomiting that is associated with surgery and cancer chemotherapy. Migraine is treated with triptans and ergot alkaloids. Cisapride, a 5-HT_4 receptor agonist, is used only compassionately to treat gastroesophageal reflux and motility disease.

Selective serotonin reuptake inhibitors (SSRIs) act to block serotonin transporters and are used to treat major depression.

25.3 **C.** Prolonged vasospasm caused by smooth muscle stimulation is a serious consequence of overdose with ergotamine. The most common adverse effects of ondansetron are headache and constipation. Serious cardiac arrhythmia is a serious adverse effect of cisapride. The major adverse effect of alosetron, a 5-HT_3 receptor antagonist, is constipation.

PHARMACOLOGY PEARLS

- Because the vasoconstrictor activity of ergotamine is long-lasting, its dose and frequency of administration must be limited.
- Ergot alkaloid agents can cause vasoconstriction and should not be used in patients with occlusive vascular disease.
- The effects of selective serotonin receptor antagonists like ondansetron seem to be enhanced with concomitant administration of dexamethasone.

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CASE 26

You are called to see a 24-year-old G_3P_3 woman who approximately 1 hour ago underwent a vaginal delivery of an 8-lb infant. The nurse is concerned that the patient is continuing to bleed more than would be expected, and that her uterine fundus does not feel firm. A brief history from the nurse reveals that the patient required IV oxytocin augmentation of her labor, but otherwise had an uncomplicated labor and delivery. Her placenta delivered spontaneously and intact. She has no significant medical history. Examination of the patient reveals her to be comfortable and cooperative but she is mildly tachycardic. Her uterine fundus is boggy and nontender on palpation. Vaginal examination shows no cervical or vaginal lacerations, but there is a steady flow of blood from the still-dilated cervix. You diagnose the patient as having a postpartum hemorrhage secondary to uterine atony and order an immediate intramuscular (IM) injection of methylergonovine.

- What is the mechanism of action of methylergonovine?
- What are the common adverse effects of methylergonovine?

ANSWERS TO CASE 26:
Ergot Alkaloids

Summary: A 24-year-old woman has a postpartum hemorrhage secondary to uterine atony. She is given an IM injection of methylergonovine.

- **Mechanism of action of methylergonovine:** α-Adrenoceptor agonist with activity on uterine smooth muscle, causing forceful and prolonged uterine contraction.
- **Side effects of methylergonovine:** hypertension, headaches, nausea, vomiting.

CLINICAL CORRELATION

Methylergonovine is an amine ergot alkaloid with relatively selective activity at uterine smooth muscle. Ergot alkaloids are structurally similar to norepinephrine, dopamine, and serotonin. They can have agonist or antagonist effects on α-adrenoceptors, dopamine receptors, and serotonin receptors. Methylergonovine acts primarily via α-adrenoceptors and 5-HT_2 receptors to cause tetanic uterine contraction. This provides its therapeutic benefit in the treatment of postpartum hemorrhage because of uterine atony. This drug can have other effects mediated by α-adrenoceptors, including acute hypertensive reactions and vasospasm. It is contraindicated in patients with uncontrolled hypertension. Other common side effects include headaches, nausea, and vomiting.

APPROACH TO:
Pharmacology of the Ergot Alkaloids

OBJECTIVES

1. Know the mechanism of action of the ergot alkaloids.
2. Know the therapeutic uses and side effects of ergot alkaloids.

DEFINITIONS

Postpartum hemorrhage: Vaginal bleeding exceeding 500 mL after a vaginal delivery or 1000 mL after a cesarean delivery. The most common etiology is uterine atony.

Migraine: A familial disorder marked by periodic, usually unilateral, pulsatile headaches that begin in childhood or early adult life and tend to recur with diminishing frequency in later life. There are two closely related syndromes comprising what is known as migraine. They are classic migraine (migraine with aura) and common migraine (migraine without aura).

DISCUSSION

Class

The ergot alkaloids are produced by the fungi *Claviceps purpurea*. There are two major families of ergots: the peptide ergots and the amine ergots, all contain the tetracyclic ergoline nucleus. The peptide ergots include ergotamine, α-ergocryptine and bromocriptine; the amine ergots include lysergic acid, lysergic acid diethylamide, ergonovine, and methysergide. The ergots have agonist, partial agonist, and antagonist actions at α-adrenergic receptors and serotonin receptors, and agonist or partial agonist actions at central dopamine receptors.

Postpartum Hemorrhage **Ergonovine** and its semisynthetic derivative, methylergonovine, cause **powerful contractions of smooth muscle;** the gravid uterus is especially sensitive to this drug. Postpartum hemorrhage is most often treated with oxytocin. In circumstances where oxytocin is not effective, methylergonovine causes forceful contractions of uterine smooth muscle that effectively stops the bleeding. This action appears to be mediated by agonist activity at α_1-adrenergic receptors and agonist action at 5-HT_2 receptors. Methylergonovine can be administered orally or IM; effects are seen in 3–5 minutes following IM administration. Acute administration of methylergonovine has few side effects.

Migraine Headache **Dihydroergotamine is useful in the prophylactic management of migraines.** It binds with high affinity to 5-$HT_{1D\alpha}$ and 5-$HT_{1D\beta}$ receptors. It also binds with high affinity to serotonin 5-HT_{1A}, 5-HT_{2A}, and 5-HT_{2C} receptors, noradrenaline α_{2A}, α_{2B}, and α_1 receptors, and dopamine D_{2L} and D_3 receptors. The therapeutic activity of dihydroergotamine in migraine is generally attributed to the agonist effect at 5-HT_{1D} receptors. Two current theories have been proposed to explain the efficacy of 5-HT_{1D} receptor agonists in migraine. One theory suggests that activation of 5-HT_{1D} receptors located on carotid and intracranial blood vessels, including those on arteriovenous anastomoses, leads to vasoconstriction, which correlates with the relief of migraine headache. The alternative hypothesis suggests that activation of 5-HT_{1D} receptors on sensory nerve endings of the trigeminal system results in the inhibition of proinflammatory neuropeptide release. Adverse effects include GI disturbances including diarrhea, vomiting, and vasospasm. The triptans—sumatriptan, rizatriptan, almotriptan, and others—are selective 5-HT_{1D} and 5-HT_{1B} receptor agonists that are also useful for treating an acute migraine headache.

Methysergide is used for **prophylaxis** of migraine. It acts as a 5-$HT_{2A,C}$ antagonist to block 5-HT mediated vasoconstriction in vascular smooth muscle. It is effective in preventing or reducing the frequency of migraines in approximately 60 percent of patients. Chronic use of methysergide is associated with **retroperitoneal fibroplasia and subendocardial fibrosis.** For this reason, drug-free periods are recommended if it is used chronically.

Endocrine Abnormalities Bromocriptine is very effective in reducing the high levels of prolactin production that occur with certain pituitary tumors. It has also been used to suppress lactation. Bromocriptine is a potent dopamine receptor

agonist, and its prolactin-suppressive actions are mediated via interaction with this receptor. Side effects are dose related and range from nausea to Parkinson-like syndrome. Bromocriptine has been associated with postpartum cardiovascular toxicity.

COMPREHENSION QUESTIONS

26.1 Methylergonovine is useful in treating postpartum hemorrhage because it does which of the following?

A. Causes forceful contractions of the myometrium
B. Causes rapid production of thrombin
C. Is a potent vasoconstrictor
D. Stimulates the activity of antithrombin III

26.2 Which of the following would be the best drug to reduce prolactin levels in a patient with a pituitary tumor?

A. Bromocriptine
B. Ergonovine
C. Ergotamine
D. Methysergide

26.3 A 35-year-old woman is noted to have dyspnea with exertion. Echocardiography identifies a restrictive cardiomyopathy with decreased flexibility of the heart. The cardiologist notes that one of his medications may be responsible. Which of the following agents is most likely the etiology?

A. Bromocriptine
B. Ergonovine
C. Ergotamine
D. Methysergide

ANSWERS

26.1 **A.** Although methylergonovine does cause vasoconstriction, its action in postpartum hemorrhage is mediated by forceful clamping of the myometrium, which restricts blood flow.

26.2 **A.** Bromocriptine is a dopamine receptor agonist that is used to treat prolactin-secreting pituitary adenomas.

26.3 **D.** Methysergide can induce a fibroelastosis of the heart, which leads to a restrictive cardiomyopathy.

PHARMACOLOGY PEARLS

- Methysergide is useful for prophylaxis of migraine headaches but has no effect on an acute episode.
- Bromocriptine is a dopamine receptor agonist and is used to treat prolactin-secreting pituitary adenomas.
- Methylergonovine is used to treat postpartum hemorrhage caused by uterine atony and causes contraction of the uterine smooth muscle.

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CASE 27

A 24-year-old G_3P_3 woman, now 90 minutes after vaginal delivery and having received an injection of methylergonovine, continues to have postpartum bleeding. Her uterus is firmer but still somewhat boggy. Her heart rate remains mildly tachycardic, but her blood pressure has gone up in response to the methylergonovine. Her examination is otherwise unchanged. You now order an IM injection of carboprost tromethamine (prostaglandin $F_{2\alpha}$, $PGF_{2\alpha}$).

- What is the therapeutic action of $PGF_{2\alpha}$ in postpartum hemorrhage?
- What is the effect of PGFs on vascular smooth muscle?
- What is the effect of PGFs on bronchial smooth muscle?

ANSWERS TO CASE 27:
Eicosanoids

Summary: A 24-year-old woman has continued postpartum hemorrhage despite ergot alkaloids.

- **Therapeutic action of $PGF_{2\alpha}$:** Causes contraction of uterine smooth muscle.
- **Effect on vascular smooth muscle:** Arteriolar vasodilation and constriction of superficial veins.
- **Effect on bronchial smooth muscle:** Smooth muscle contraction.

CLINICAL CORRELATION

Eicosanoids are a large and varied group of autocoids with effects on most tissues in the body. They are derivatives of eicosanoic acids and are synthesized throughout the body. They typically have short plasma half-lives (seconds) and are catabolized mainly in the lung. There is no common mechanism of eicosanoid action. Specific cell surface receptors mediate activities of each class of eicosanoid and many different second messenger pathways are involved. $PGF_{2\alpha}$ is produced via the prostaglandin H synthase (cyclooxygenase) pathway. It causes arteriolar vasodilation, superficial vein constriction, and bronchial smooth muscle contraction and increases the rate of longitudinal muscle contraction in the GI tract. It causes strong contraction of uterine smooth muscle in the pregnant uterus. This effect mediates its primary therapeutic use, the treatment of postpartum hemorrhage. Because of the risk of bronchospasm, its use is contraindicated in asthmatics. It can cause nausea, vomiting, diarrhea, and cramps as a result of its effect on the GI tract.

APPROACH TO:
Pharmacology of the Eicosanoids

OBJECTIVES

1. Know the pathways of eicosanoid synthesis.
2. Know the actions of eicosanoids on tissues throughout the body.
3. Know the therapeutic uses, adverse effects, and contraindications to the use of eicosanoids.

DEFINITIONS

Eicosanoids: Metabolites of 20-carbon fatty acids.

Prostanoids: Prostaglandins and thromboxanes.

COX: Cyclooxygenase, rate-limiting enzymes (COX-1 and COX-2) in prostaglandin biosynthesis.

HETE: Hydroxyeicosatetraenoic acid.

EET: Epoxyeicosatrienoic acid.

DISCUSSION

Class

The **eicosanoids** are **fatty acid metabolites** that include **prostaglandins, thromboxanes, HETEs,** and **EETs.** These small molecules affect nearly every physiologic system, including blood flow, especially in the kidney, airway diameter, inflammation, ovulation, and uterine smooth muscle tone. The eicosanoids are metabolites of **20-carbon fatty acids, mostly arachidonic acid.** A substrate pool of arachidonic acid is stored as part of the lipids in the plasma membrane. Figure 27–1 outlines the two

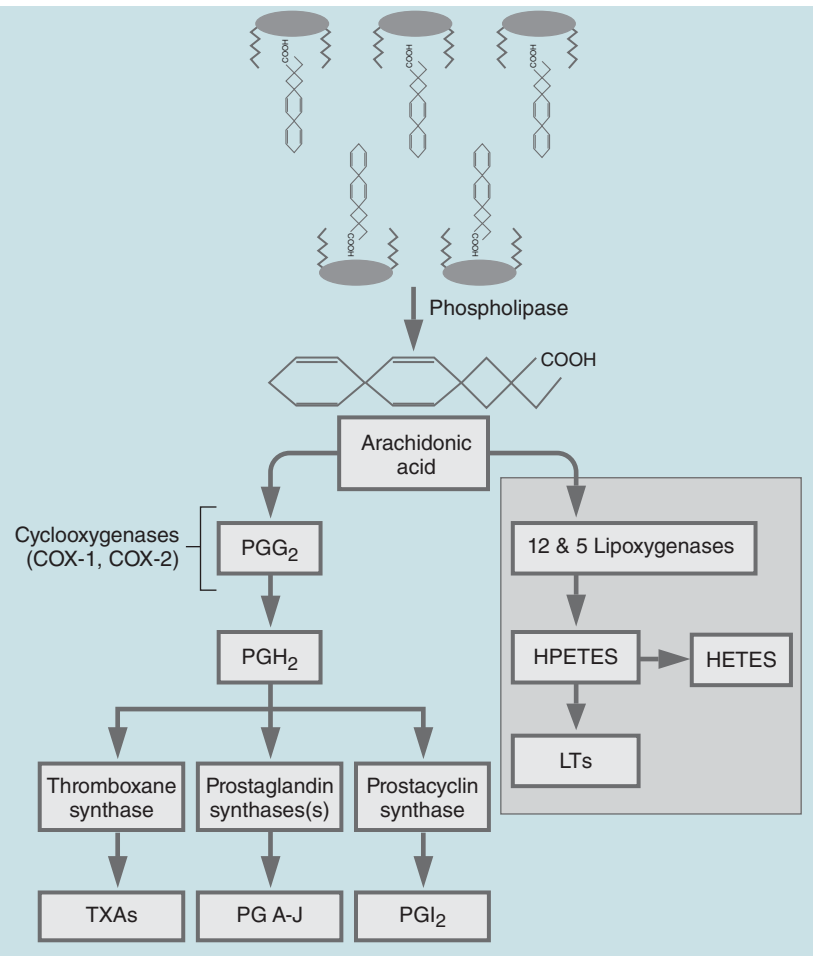

Figure 27–1. Synthesis of eicosanoids.

major biosynthetic routes of eicosanoic metabolites. Most of the free arachidonic acid in cells is liberated from the plasma membrane phospholipid by phospholipase A_2. A minor amount can be liberated from phosphatidylinositides by the action of phospholipase C and diglyceride lipase. The free arachidonic acid is metabolized by either **cyclooxygenase** isoform producing prostaglandins and thromboxane, or by **lipoxygenases** to form the **HETEs** and **leukotrienes.** There are two isoforms of cyclooxygenases that catalyze the same reaction.

Cyclooxygenase type 1 (COX-1) is fairly widely distributed in the **stomach, kidneys, and connective tissues.** COX-1 is expressed in a constitutive manner. **COX-2** is also expressed in numerous tissues including the **GI tract, kidneys, ovaries,** and **connective tissues.** Basal cyclooxygenase type 2 (COX-2) expression is very low, but it is highly induced by cytokines, growth factors, and serum factors. The cyclooxygenases perform two catalytic steps: a **cyclooxygenase reaction that introduces oxygen and a peroxidase** reaction that yields PGH_2, the **immediate precursor to all prostaglandins and thromboxane.** PGH_2 is further metabolized to prostaglandins or thromboxane depending on the tissue. **Platelets contain predominantly thromboxane synthase and produce thromboxane A_2; endothelial cells** contain predominantly **prostacyclin synthase and produce PGI_2;** other cells contain specific **prostaglandin synthases** and produce prostaglandins A–J.

Lymphocytes and other myeloid cells contain **lipoxygenases** that convert PGH_2 into HETEs or leukotrienes via an unstable HETEs intermediate. Leukocytes express both 5-lipoxygenase and 12-lipoxygenase and produce the corresponding HETEs and the leukotrienes. Platelets express only 12-lipoxygenase and produce 12-HETE.

Two other metabolic pathways have been shown to produce other arachidonate metabolites. Free arachidonate can be metabolized by members of the P450 family to the EETs that have potent vascular and renal effects. Arachidonate acid intact on a phospholipid can be acted on by free radicals to produce the isoprostanes via a non-enzymatic pathway. The isoprostanes may be important in inflammation but their physiologic role is still under investigation. Eicosanoids have a myriad of effects; only those of pharmacologic relevance will be discussed here.

Vascular System **PGE_2 and PGI_2 (prostacyclin) are potent vasodilators** in most vascular beds. PGI_2 is about five times more potent than PGE_2 in reducing blood pressure. $PGF_{2\alpha}$ typically causes vasoconstriction especially in pulmonary arteries and veins, and vasoconstricts superficial veins. **Thromboxane A_2 is a potent vasoconstrictor** and is a smooth muscle cell mitogen.

Other Smooth Muscle **PGEs relax bronchial and tracheal smooth muscle.** The response of uterine myometrium is complex with low doses of PGE_2 causing contraction and higher doses causing relaxation. In the GI tract, PGEs relax circular smooth muscle but the longitudinal muscle is contracted. $PGF_{2\alpha}$, PGD, and TXA_2 cause bronchoconstriction in the airways and contraction of GI smooth muscle.

Gastrointestinal Secretion PGEs and PGI_2 inhibit gastric acid and pepsin production and increase mucus production; these actions are **cytoprotective** in the upper GI tract.

Kidney Prostaglandins are important local regulators of renal blood flow. PGEs and PGI_2 increase renal blood flow and diuresis without changing the glomerular filtration rate. TXA_2 decreases renal blood flow and glomerular filtration rate.

Pharmacologic Uses of Eicosanoids

PGE_1 can be used in neonates to maintain patency of the ductus arteriosus. Infants born with certain congenital heart abnormalities depend on a patent ductus to maintain adequate pulmonary blood flow. **PGE_1** is used to temporarily maintain patency until surgery can be performed. **PGE_1,** because of its vasodilatory action, can be injected into the corpus cavernosum of the **penis to induce erection.** This use has been largely supplanted by the **phosphodiesterase V inhibitors such as sildenafil. PGE_1 analogs have also been used for cytoprotection of NSAID-induced gastric and peptic ulcers.** This is based on the protective action mediated by the reduction in acid and pepsin production and increased mucus production produced by PGE_1. PGE_1, PGE_2, and PGI_2 and their congeners have also been used to treat peripheral occlusive vascular disease and have been used for treating Raynaud disease and arteriosclerosis obliterans. Because of its effect to inhibit platelet aggregation and its short half-life, PGI_2 can be used during dialysis instead of heparin. It is one of the few treatments for pulmonary arterial hypertension.

Uterine contractions are stimulated by 15-methyl-$PGF_{2\alpha}$. It can be used to control persistent postpartum hemorrhage secondary to uterine atony that is unresponsive to other drugs. 15-methyl-$PGF_{2\alpha}$ can be used in the first and second trimester to induce abortion. PGE_2 congeners are used to facilitate cervical ripening and for the induction of labor. PGE_2 is combined with the antiprogestin RU-486 (mifepristone) to induce first-trimester abortion. Side effects are usually nausea and vomiting. It is contraindicated in asthmatics because of its bronchoconstrictive activities.

Structure

Prostaglandins are derived by metabolism of the 20-carbon fatty acid arachidonic acid.

Mechanism of Action

There are a number of specific membrane receptors that mediate the action of the prostaglandins. There are four prostaglandin E receptors (EP_1–EP_4), two prostaglandin F receptors (FPA and FPB), one prostaglandin I_2 receptor (IP), two thromboxane receptors (TP_α and TP_β), and two prostaglandin D receptors (DP and $CRTH_2$). These receptors are coupled to increases or decreases in cAMP, and increases in inositol-3 phosphate.

Administration

Most prostaglandins or their analogs are administered by local instillation (eg, vaginal or cervical gels or suppositories, penile injection) or continuous infusion. Misoprostol, a PGE_1 analog, is available for oral administration.

Pharmacokinetics

Prostaglandins are rapidly absorbed and inactivated in lung, liver, and kidney. Both the natural prostaglandins and their analogs have a very short half-life (typically seconds to minutes).

COMPREHENSION QUESTIONS

27.1 Which of the following enzymes do leukotrienes require for their biosynthesis?

A. COX-1
B. COX-2
C. 5-Lipoxygenase
D. 8-Lipoxygenase

27.2 PGI_2 can be used to achieve which of the following?

A. Cause peripheral vasoconstriction
B. Control bleeding from the uterine artery
C. Facilitate blood clotting
D. Treat occlusive vascular disease

27.3 A 38-year-old woman is taking ibuprofen for severe dysmenorrhea but develops epigastric pain. The physician prescribes a medication to prevent gastritis. Which of the following best describes the medication?

A. PGE_1 analog
B. PGE_1 antagonist
C. PGE_2 analog
D. PGE_2 antagonist
E. PGI_2 analog
F. PGI_2 antagonist

ANSWERS

27.1 **C.** Production of leukotrienes requires 5-lipoxygenase.

27.2 **D.** PGE_2 and PGI_2 are vasodilators in all vascular beds.

27.3 **A.** PGE_1 analog, misoprostol, is used to prevent NSAID-associated gastritis.

PHARMACOLOGY PEARLS

- PGE_1 and PGI_2 can be used to produce relatively local vasodilation.
- PGE_2 and $PGF_{2\alpha}$ have obstetric uses to control uterine bleeding and to hasten parturition.
- 15-Methyl-$PGF_{2\alpha}$ stimulates uterine contractions. It can be used to control persistent postpartum hemorrhage.
- Thromboxane is a potent vasoconstrictor.

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CASE 28

A 16-year-old female comes to the physician's office because of menstrual cramps. She had menarche at age 13. Her menses lasts for 4–5 days, and she has 28-day cycles. For the first 2–3 days of her menses she states that she has very bad cramping. The cramps have occurred since menarche and seem to have worsened in the past year. They have been so bad at times that she has missed school and has not been able to participate in her after-school sports. She has been taking acetaminophen and over-the-counter "menstrual cramp" pills without adequate relief. She has no significant medical history, takes no medications regularly, and is not sexually active. Her examination is normal. You assess the problem as primary dysmenorrhea and prescribe diclofenac to be used on an as-needed basis.

- What are the therapeutic effects of nonsteroidal anti-inflammatory drugs (NSAIDs)?
- What is the mechanism of the anti-inflammatory action of NSAIDs?

ANSWERS TO CASE 28:
Nonsteroidal Anti-Inflammatory Drugs

Summary: A 16-year-old female with dysmenorrhea is prescribed diclofenac (Voltaren-XR).

- **Effects of NSAIDs:** Anti-inflammatory, analgesic, and antipyretic.
- **Mechanism of action:** Anti-inflammatory effect primarily resulting from inhibition of cyclooxygenase 1 and/or cyclooxygenase 2; may also involve interference with other mediators of inflammation, modulation of T-cell function, stabilization of lysosomal membranes, and inhibition of chemotaxis.

CLINICAL CORRELATION

NSAIDs are widely used for acute and chronic conditions that cause pain, injury, inflammation, or fever. They are available over-the-counter and by prescription. The anti-inflammatory effect is a result of the inhibition of cyclooxygenase (COX), which converts arachidonic acid to prostaglandins. There are two major subtypes of the COX enzyme, with the COX-2 subtype primarily mediating the pain and inflammation responses in tissues throughout the body. COX-1 has significant activity in producing prostaglandins that appear to protect the GI mucosal lining. **Aspirin irreversibly inactivates both COX-1 and COX-2,** whereas all other **NSAIDs are reversible inhibitors of one or both of these enzymes.** The analgesic effect of these medications is thought to be related to the peripheral inhibition of prostaglandin production, and central inhibition of the transmission of pain stimuli as well. The antipyretic effect is thought to involve inhibition of IL-1- and IL-6-induced production of prostaglandins in the hypothalamus affecting the thermoregulatory system, resulting in vasodilation and increased heat loss. NSAIDs are metabolized in the liver and excreted by the kidney. They exhibit cross-sensitivity with each other and with aspirin. All NSAIDs can cause non-dose-related episodes of acute renal failure and nephrotic syndrome. They should be used with caution in those with renal insufficiency or in patients taking other potentially nephrotoxic agents. Aspirin and NSAIDs that nonselectively inhibit both COX-1 and COX-2 commonly produce GI disturbances and ulceration. They are contraindicated in persons with known peptic ulcer disease. Newer agents with higher selectivity for COX-2 inhibition have fewer GI side effects and may reduce, but not eliminate the rate of NSAID-related gastric ulcers. All of the NSAIDs may increase the risk of cardiovascular disease.

APPROACH TO:

Pharmacology of NSAIDs

OBJECTIVES

1. Know the mechanism of action of aspirin and other NSAIDs.
2. Know the therapeutic uses of NSAIDs.
3. Know the adverse effects, toxicities, and contraindications to NSAID use.

DEFINITIONS

Inflammation: A local response to cellular injury that is marked by capillary dilatation, leukocytic infiltration, redness, heat, pain, and swelling.

Familial adenomatous polyposis (FAP): A genetic disorder leading to abnormal growths in the colon.

DISCUSSION

Class

(See Case 27 on eicosanoids for a description of the biosynthesis of the prostaglandins and leukotrienes.) NSAIDs are among the most widely used drugs and are available in various formulations both over-the-counter and by prescription. They are widely used for the relief of pain and fever and to reduce inflammation. There are more than 23 NSAIDs available, and they represent a number of structural classes. Table 28–1 summarizes this class of drugs. They are all small acidic compounds. All are orally active with some pharmacologic differences but they all share the following:

Analgesic activity. Effective against pain of low-to-moderate intensity. Lower maximal effects compared to opioids, but no CNS liability.

Anti-inflammatory activity. It is their chief clinical application. They provide symptomatic relief only.

Antipyretic activity. Act to alter hypothalamic set-point. **Gastric and intestinal ulceration.** Two mechanisms include local irritation caused by a particulate acidic drug, and inhibition of prostaglandins, which exert a cytoprotective effect.

Table 28–1 • CLASSES OF NSAIDS

Carboxylic Acids			Pyrazolones	Oxicams
Salicylates	Acetic acids	Propionic acids	Phenylbutazone	Piroxicam
Acetylsalicyclic acid	Indomethacin	Ibuprofen	Apazone	Meloxicam
Salicyclic acid	Diclofenac	Naproxen		
	Sulindac	Ketoprofen		
	Tolmetin	Pranoprofen		
		Miroprofen		

Carboxylic Acids **The salicylates, acetylsalicylic acid (ASA, aspirin), and sodium salicylate** have been used for hundreds of years for their analgesic properties. **ASA acts to covalently and irreversibly inhibit both COX-1 and COX-2.** COX-1 becomes acetylated at a serine in the cyclooxygenase-active site, rendering the enzyme inactive. COX-2 is also covalently modified but at a different serine residue. This also eliminates cyclooxygenase activity and alters COX-2 to produce 15-HETE. 15-HETE can be further metabolized to a potent **anti-inflammatory** compound, 15-epilipoxin A_4. Some of the anti-inflammatory activity of aspirin might be mediated by this metabolite. Inhibition of cyclooxygenase activity of both COX isoforms decreases prostaglandin and thromboxane production, but does not affect the production of eicosanoids through the lipoxygenase pathway. Sodium and magnesium salicylate lack the acetyl group that modifies the COXs and are much weaker anti-inflammatory agents. Their mechanism of action may be to reduce free radical production that is necessary to activate the cyclooxygenases.

Aspirin can be used to reduce pain, temperature, and inflammation. The anti-inflammatory properties make it useful in rheumatoid arthritis (RA), rheumatic fever, and other diseases that produce joint pain.

The **adverse effects of aspirin are dose related. At low doses,** most adverse effects are confined to the **GI tract, commonly gastritis.** At **higher** doses patients suffer **"salicylism," tinnitus, vomiting, and vertigo.** Serious aspirin overdose affects the medulla directly and **depresses respiration.**

Acetic and Propionic Acids **Indomethacin, ibuprofen, diclofenac, and naproxen** are other important NSAIDs. Although they reduce prostaglandin production by **inhibiting COX-1 and COX-2,** the mechanism of this inhibition is different from aspirin. These drugs are **reversible inhibitors** of the enzyme and appear to act by interfering with the **binding of arachidonate.** All have been approved for rheumatic disorders, osteoarthritis, localized musculoskeletal pain, dysmenorrhea, and headache. All are readily absorbed from the GI tract. Indomethacin and diclofenac are the most potent of these drugs in inhibiting cyclooxygenase. **Indomethacin also has the highest incidence (35–50%) of adverse effects, most commonly GI. Indomethacin** has been found to produce **ulceration of the upper GI tract.** Naproxen and ibuprofen are also associated with frequent GI adverse effects but are less severe and better tolerated. **All of the NSAIDs can produce renal toxicities including acute renal failure.**

Specific COX-2 Inhibitors Considerable effort has gone into the development of agents that **specifically inhibit COX-2** compared to COX-1. In theory, such agents would be efficacious for **treating inflammatory states but have fewer adverse effects,** especially in the GI tract because COX-1 would still be able to provide cytoprotection. Two clinical trials support this notion, but these drugs still produce adverse effects in the GI tract.

Celecoxib (Celebrex) is the only specific COX-2 inhibitor in the US market. Rofecoxib (Vioxx) and valdecoxib (Bextra) were removed from the market due to an increase in risk of cardiovascular disease and stroke. Subsequent meta-analysis of many studies has led to the conclusion that chronic administration of any NSAID increases the risk of MI and stroke. All NSAIDs now carry a black box warning to

this effect. Celecoxib is useful in treating osteoarthritis, RA, ankylosing spondylitis, dysmenorrhea, acute pain, and pain caused by migraine. **Celecoxib is approved for the treatment of FAP.** Adverse effects are diminished with COX-2-specific inhibitors, but there are still significant side effects. Rare instances of serious stomach and intestinal bleeding have been reported. Hepatotoxicity and acute renal failure have also occurred. Less serious side effects include dyspepsia, diarrhea, peripheral edema, and dizziness.

Other Agents **Acetaminophen** is a **non-anti-inflammatory** analgesic agent. It is about as effective at reducing fever and as an analgesic as aspirin, but it lacks anti-inflammatory activity and does not inhibit platelet aggregation. It was considered relatively safe in pregnancy, but studies have suggested an increased risk of asthma and cryptorchidism in children of treated mothers. The most important toxicity of acetaminophen is hepatotoxicity. This is caused by the metabolism of the drug to *N*-acetyl-p-benzoquinoneimine (NAPB), which is usually **eliminated by hepatic conjugation with glutathione.** Toxic levels of acetaminophen deplete glutathione and NAPB accumulates to toxic levels. Other adverse effects include skin rash and mild dyspepsia.

COMPREHENSION QUESTIONS

28.1 A 54-year-old man asks about how to reduce the risk of MI. Which of the following is the most effective in reducing risk of myocardial infarction?

A. Acetaminophen
B. Aspirin
C. Celecoxib
D. Ibuprofen

28.2 Which of the following is the advantage of specific cyclooxygenase-2 (COX-2) inhibitors?

A. Decreased GI side effects
B. Decreased vasoconstrictor activity
C. Increased anti-inflammatory activity
D. Increased inhibition of platelet aggregation

28.3 A 26-year-old woman takes a "handful" of acetaminophen in a suicide attempt. At the emergency department, it is determined that she has taken enough to be potentially harmful. Which of the following is the best treatment for this patient?

A. Calcium gluconate
B. IgG against acetaminophen
C. *N*-acetylcysteine
D. Penicillamine

ANSWERS

28.1 **B.** Aspirin. Because aspirin irreversibly inhibits cyclooxygenase, it effectively eliminates thromboxane production by platelets. It can do this at low doses that do not impair the production of beneficial PGI_2 by endothelial cells.

28.2 **A.** In theory, inhibition of COX-2 would reduce inflammation and pain while leaving the cytoprotective actions of COX-1 intact. However, the two enzymes appear to overlap in their functions to a considerable degree.

28.3 **C.** Excess acetaminophen is metabolized in the liver via the mixed function oxidase P450 system to a toxic metabolite, NAPB, which has an extremely short half-life and is rapidly conjugated with glutathione, a sulfhydryl donor, and removed from the system. Under conditions of excessive NAPB formation or reduced glutathione stores, NAPB is free to covalently bind to vital proteins and the lipid bilayer of hepatocytes; this results in hepatocellular death and subsequent centrilobular liver necrosis. The antidote for acetaminophen poisoning is ***N*-acetyl-L-cysteine** (NAC), which prevents the formation and accumulation of NAPB, increases glutathione stores, combines directly with NAPB as a glutathione substitute, and enhances sulfate conjugation.

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CASE 29

A 58-year-old man presents for follow-up of gout. He has had multiple episodes of gouty arthritis, primarily in the great toe. Each episode has been successfully treated with oral anti-inflammatory medications. He takes no medications regularly and has a normal examination today. Laboratory studies following his last episode showed an elevated uric acid level and normal renal function. A 24-hour urine collection showed normal excretion of uric acid. You prescribe allopurinol to be taken daily in an effort to lower his uric acid level and prevent recurrent gout episodes.

- Which medications are used for the treatment of acute gout?
- Which medications are used for the treatment of chronic gout?
- What is the mechanism of action of allopurinol?

ANSWERS TO CASE 29:
Medications Used to Treat Gout

Summary: A 58-year-old man with hyperuricemia and recurrent gout is prescribed allopurinol.

- **Drugs for the treatment of acute gout:** Nonsteroidal anti-inflammatory agents (NSAIDs), colchicine, corticosteroids, pegloticase.
- **Drugs for the treatment of recurrent gout:** Probenecid, sulfinpyrazone, allopurinol, febuxostat.
- **Mechanism of action of allopurinol:** Inhibition of xanthine oxidase, an enzyme that converts hypoxanthine to xanthine and xanthine to uric acid.

CLINICAL CORRELATION

Allopurinol is a medication used in clinical practice to **lower uric acid production.** Uric acid is the end product of purine metabolism. The **enzyme xanthine oxidase converts hypoxanthine to xanthine and xanthine to uric acid.** Allopurinol and its metabolite, alloxanthine, inhibit the synthesis of uric acid by inhibiting xanthine oxidase. Allopurinol may precipitate acute gout when therapy is initiated. Colchicine may be coadministered for the first week of allopurinol therapy to try to reduce the risk of an acute gout flare. Its primary side effects are GI disturbance and rash. There is a very rare, but potentially life-threatening, hypersensitivity reaction that may cause fever, bone marrow suppression, hepatic dysfunction, and renal failure.

APPROACH TO:
Medications for Gout

OBJECTIVES

1. Know the primary drugs used for gout and their mechanisms of action.
2. Know the adverse effects and contraindications to their usage.

DEFINITIONS

Prophylactic: Prevention of a disease or adverse event.

Gout: Condition of painful deposits of urate crystals in the joints and other parts of the body such as the ear pinna.

DISCUSSION

Class

Allopurinol and febuxostat (Uloric) are prophylactic drugs that reduce the biosynthesis of uric acid. In this manner, **serum uric acid levels are typically reduced,**

and the formation of **inflammatory tophi within joints is reduced.** Evidence shows that keeping the serum uric acid less than 6–6.5 may reduce future attacks. Febuxostat is more potent, less allergenic, and more specific than allopurinol, which inhibits enzymes in purine-pyrimidine biosynthesis other than xanthine oxidase. These drugs provide a useful **long-term therapy** for patients with chronic gouty arthritis but should not be used during an acute attack. Allopurinol is also indicated for the **treatment of hyperuricemia secondary to blood dyscrasias, especially during cancer chemotherapy,** and for the prophylaxis of both uric acid and calcium oxalate renal stone formation that is typically associated with hyperuricemia. Allopurinol is useful in patients with **recurrent renal stones** or with renal impairment or those that do not respond to probenecid. Patients treated with allopurinol should have adequate renal secretion of uric acid. **Adverse effects include diarrhea, nausea, and vomiting, and an allergic skin reaction is reported in 3 percent of patients.** On initial use of allopurinol, uric acid is mobilized from tissues and joints and this may **precipitate an acute gouty attack.**

Structure

Allopurinol is a structural analog of xanthine, and febuxostat is a thiazole carboxylic acid noncompetitive inhibitor of the enzyme.

Mechanism of Action

Allopurinol and febuxostat inhibit xanthine oxidase (Figure 29–1) and reduce the biosynthesis of urate by affecting two steps in the conversion of purines to uric acid. These drugs also increase the reutilization of xanthine and hypoxanthine via hypoxanthine guanine phosphoribosyltransferase (HGPRT) to increase nucleic acid and

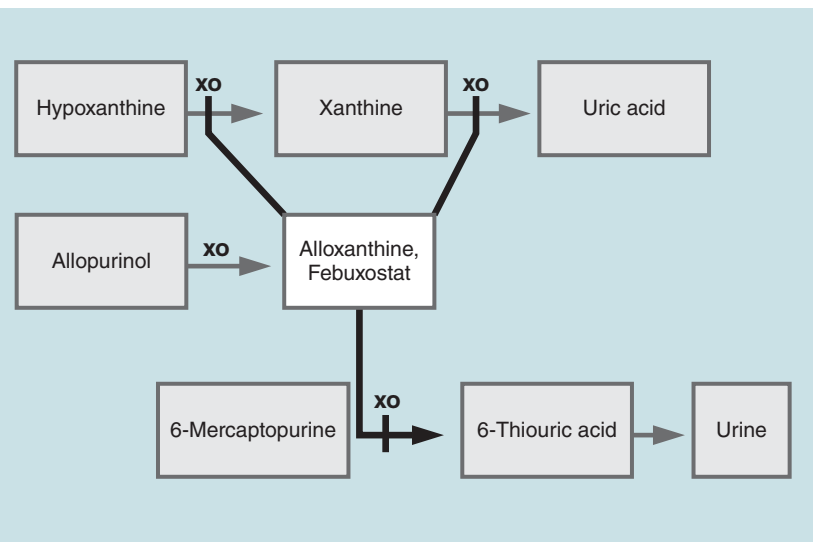

Figure 29–1. Uric acid pathway. XO = xanthine oxidase, which is blocked by allopurinol and febuxostat.

nucleotide synthesis. This causes a negative feedback that decreases de novo purine biosynthesis. These actions decrease both serum and urine uric acid. Xanthine oxidase is responsible for inactivation of azathioprine and 6-mercaptopurine, and for activation of 5-fluorouracil. Inhibition of the enzyme by allopurinol or febuxostat can increase toxicity of the former and decrease the effectiveness of the latter.

Administration

Allopurinol and febuxostat have good oral bioavailability and bioavailability is decreased by food.

Pharmacokinetics

A significant reduction on serum uric acid concentration usually requires 2–3 days, and the reduction of serum urate to normal levels may take 1–3 weeks. Allopurinol has a half life of 1–3 hours and the half-life of its active metabolite alloxanthine is 12–30 hours, permitting once-a-day dosing. Approximately 80 percent of allopurinol is eliminated by the kidney as alloxanthine and the remainder is eliminated in the feces. Febuxostat has a half-life of 5–8 hours and is eliminated mostly by the liver.

Other Drugs Used to Treat Gout

The xanthine oxidase inhibitors are useful in managing gout in patients with normal levels of uric acid excretion. In those patients with gout secondary to impaired renal excretion of uric acid (see Case 8), **probenecid or sulfinpyrazone** is more effective. These **drugs block renal reabsorption of uric acid and thereby increase excretion. The pain associated with acute attacks of gout are typically treated with NSAIDs** or **colchicine.** Virtually all NSAIDs have been used successfully to treat the pain associated with gout, but **indomethacin and sulindac remain the most frequently used. Aspirin should not be used to treat gout because it impairs renal excretion of uric acid. Colchicine** is particularly effective in treating gout. Colchicine **binds to microtubules** and impedes cellular movement. This impairs the mobility of leukocytes, which play an important role in the inflammatory process. Colchicine also decreases the production of leukotriene B_4. The most common adverse effects of colchicine are GI with nausea, vomiting, and diarrhea and, rarely, bone marrow depression. In patients with refractory gout unresponsive to the above, **pegloticase has been effective. Pegloticase (Krystexxa)** is a recombinant uricase (which is not expressed in humans) that is administered by infusion every 2 weeks. It can reduce serum urate in hours.

COMPREHENSION QUESTIONS

29.1 A 48-year-old man is diagnosed with gout. Allopurinol is useful in treating gout because of which of the following property?

A. It increases the catabolism of uric acid.

B. It increases the degradation of uric acid.

C. It decreases the production of uric acid.

D. It increases renal excretion of uric acid.

29.2 Colchicine is especially useful in treating an acute attack of gout because it achieves which of the following?

A. Decreases uric acid deposition
B. Is potent anti-inflammatory agent
C. Impairs leukocyte migration
D. Increases the solubility of uric acid

29.3 A 44-year-old man is suffering from recurrent gouty arthritis. His serum uric acid level is elevated, and you prescribe allopurinol. Within 1 week of the allopurinol, he develops a painful episode that "feels like gout." Which of the following is the best explanation?

A. The patient is resistant to the allopurinol and should be placed on another medication.
B. The patient likely has an arthritis syndrome produced by allopurinol and should have an antinuclear antibody (ANA) drawn.
C. The patient likely developed acute gout as a result of mobilization of the urate from joints and tissues.
D. This likely represents a drug-drug interaction, and so the allopurinol should be discontinued.

29.4 A 61-year-old male patient has 5–6 painful gouty attacks every year despite being treated with febuxostat. He is highly allergic to probenecid. Which of the following would be the best course of treatment for this patient?

A. NSAIDs at maximal doses
B. Pegloticase
C. Sulfinpyrazone
D. Allopurinol

ANSWERS

29.1 **C.** The mechanism of action of allopurinol is to decrease the production of uric acid.

29.2 **C.** Impairing leukocyte migration reduces the inflammation associated with a gouty attack.

29.3 **C.** The patient likely developed an acute episode of gout as a result of the mobilization of urate from joints and tissues, a phenomenon commonly seen with initiation of allopurinol.

29.4 **B.** Pegloticase is a porcine recombinant uricase, which metabolizes urate to the water-soluble allantoin. It is highly effective in refractory patients.

PHARMACOLOGY PEARLS

- Allopurinol and febuxostat can precipitate an acute gouty attack. Initial therapy should be combined with an NSAID or colchicine to avoid this effect.
- Uric acid is the end product of purine metabolism.
- Allopurinol and febuxostat lower uric acid production by inhibiting the enzyme xanthine oxidase, which converts hypoxanthine to xanthine and xanthine to uric acid.

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CASE 30

A 40-year-old female with no known past medical history other than suspected rheumatoid arthritis (RA) presents for evaluation of her pain. Patient reports morning stiffness, swelling and tenderness of her joints in her hands, shoulders, knees for over 6 months. She also reports fatigue and a maternal family history of rheumatoid arthritis. She brought in her old records which show laboratory and clinical criteria sufficient for the diagnosis of rheumatoid arthritis. She has not been following up with her primary care physician or her rheumatologist and has been trying to self manage with over the counter ibuprofen and acetaminophen. On examination she has synovitis of both hands, wrists, shoulders, and knees. She has some early changes of RA, such as ulnar deviation of the digits of her hands, and a few rheumatoid nodules on her arms. Based on the history and examination you diagnose her with an acute exacerbation of her RA. You also explain to her that her overall disease is not being adequately managed. Hence, you start her on oral prednisone and methotrexate.

- What is the mechanism of immune suppression mediated by glucocorticoids?
- What is the mechanism of action of methotrexate?

ANSWERS TO CASE 30:
Agents Used to Treat Rheumatoid Arthritis

Summary: A 40-year-old woman with worsening rheumatoid arthritis (RA) is prescribed corticosteroids and methotrexate.

- **Mechanism of immune suppression by glucocorticoids:** Interference with cell cycle of activated lymphoid cells and activation of apoptosis in some lymphoid lines.
- **Mechanism of action of methotrexate:** Inhibition of deoxyribonucleic acid (DNA) synthesis by inhibition of dihydrofolate reductase. Inhibits replication and function of T cells and possibly B cells.

CLINICAL CORRELATION

RA is an autoimmune disorder in which the body's immune system attacks its own synovium. This causes joint stiffness, swelling and, if unchecked, joint destruction and disfigurement. Several immunosuppressive agents have been used with success in the treatment of RA. Glucocorticoids are used both for their anti-inflammatory and immunosuppressive effects. They are thought to interfere with the cell cycle of activated lymphoid cells and may activate apoptosis in some lymphoid lines. Its long-term use is limited by multiple side effects and toxicities, including induction of a Cushingoid syndrome, glucose intolerance, and reduction in bone density. Methotrexate is a cancer chemotherapeutic agent that also has immunosuppressive effects. It is a folate analog that interferes with DNA synthesis by inhibition of the dihydrofolate reductase enzyme. Its immunosuppressive effect is mediated through its inhibition of the replication and function of T, and possibly B, lymphocytes. Methotrexate can cause hepatotoxicity, bone marrow suppression, and severe GI side effects.

APPROACH TO:
Pharmacology of Agents Used in RA

OBJECTIVES

1. Know the agents used for RA and their mechanisms of action.
2. Know the toxicities and adverse effects of agents used for RA.

DEFINITIONS

Rheumatoid arthritis: Chronic disease that is characterized especially by pain, stiffness, inflammation, swelling, and sometimes destruction of joints.

Osteoarthritis: Arthritis characterized by degenerative and sometimes hypertrophic changes in the bone and cartilage of one or more joints and a progressive wearing

down of apposing joint surfaces with consequent distortion of joint position usually without bone stiffening.

DISCUSSION

Class

Rheumatoid arthritis is caused by an **inappropriate immune response** that results in **chronic inflammation in and around joints.** The chronic inflammatory process includes the production of a number of **cytokines and inflammatory mediators** that cause **destruction of cartilage within the joint.** Pharmacologic treatment of RA includes **treatment of the acute pain, treatment of the inflammation, and inhibition of the immune system.**

Glucocorticoids such as prednisolone or cortisone are potent anti-inflammatory agents and are also **immunosuppressive.** Glucocorticoids may be administered orally or injected into an affected area. Drugs with an **11-keto group** on the steroid nucleus (cortisone or prednisone) are converted to **11-hydroxyl group** in the liver (to give cortisol and prednisolone). Other synthetic corticosteroids include dexamethasone, betamethasone, and triamcinolone. Various chemical substitutions within these drugs decrease first-pass inactivation by the liver, decrease binding to plasma proteins such as corticosteroid-binding globulin (CBG), and increase the affinity of the drug for its receptor. The actions of glucocorticoids are mediated by a **specific nuclear receptor, the glucocorticoid receptor (GR).** Receptor activation occurs on drug binding, which ultimately leads to increased or decreased transcription of specific genes. The **anti-inflammatory action of the glucocorticoids** is a result, in part, of **induction of annexin-1 (also known as macrocortin),** which is a **specific inhibitor of phospholipase A_2, and inhibits the transmigration of leukocytes.** This **decreases the production of prostaglandins and the inflammatory process.** In addition, the production of a number of cytokines including IL-1, IL-2, IL-6, and TNF-α is decreased by glucocorticoids. This is caused in part by the induction of apoptosis in lymphocytes and leukocytes. Thus the anti-inflammatory and immunosuppressive actions of the glucocorticoids are closely linked. Glucocorticoids are potent inhibitors of cell-mediated immunity but have little effect on humoral immunity.

Glucocorticoids are useful in the management of inflammation in RA, bursitis, lupus erythematosus, nephrotic syndrome, and ulcerative colitis. Glucocorticoids are also used to treat hypersensitivity reactions and allergic reactions and to reduce organ or graft rejection.

The use of **glucocorticoids** is limited by a number of **adverse effects.** Most of these adverse effects are predictable as exaggerated physiologic effects. **Suppression of the pituitary-adrenal axis, hyperglycemia, increased protein metabolism, altered fat metabolism, and increased salt retention (a mineralocorticoid effect)** are frequently seen. **Osteoporosis and peptic ulcers** can be induced by glucocorticoids, and increased susceptibility to **infections** and **poor wound healing** also occur.

Methotrexate is a **folate analog that inhibits dihydrofolate reductase.** This enzyme is responsible for the production of tetrahydrofolate cofactors necessary for purine and thymidylate biosynthesis. Inhibition of the enzyme leads to impaired

DNA synthesis, which has the greatest impact on rapidly dividing cells. Methotrexate is **immunosuppressive,** and this activity has led to its use in RA, psoriasis, and other autoimmune disorders. Its use as an **anticancer agent** includes childhood acute lymphoblastic leukemia, lymphoma, and osteogenic sarcoma. Serious adverse effects associated with methotrexate include **myelosuppression,** producing severe leukopenia, bone marrow aplasia, and thrombocytopenia. **GI effects** are common with nausea and vomiting, as well as mouth sores or ulcers. Hepatotoxicity, including acute elevations in transaminase levels, fibrosis, and cirrhosis, has been reported. Pulmonary effects include a nonproductive cough and pneumonitis. Methotrexate is a teratogen contraindicated in pregnancy.

More disease-specific approaches in treating RA have led to the development of disease-modifying antirheumatic drugs **(DMARDs).**

Recent evidence supports a central role of **tumor necrosis factor alpha** (TNF-α) in the pathogenesis of RA. **TNF-α appears responsible for much of the tissue injury in the disease.** Based on these observations, two new classes of drugs have been developed that specifically target the TNF pathway. One class of drugs is **antibodies specific for human TNF-α.** These antibodies interact with TNF-α and block its ability to interact with TNF-α receptors. **Infliximab** is a chimeric antibody containing a human constant region and murine variable regions. It is administered by infusion approximately once every 8 weeks. Infliximab is also indicated in refractory luminal and fistulizing Crohn's disease. **Adalimumab** is a similar, fully human anti-TNF-α antibody that is self-injected twice weekly. **Etanercept** is a fusion protein created by combining the ligand-binding portion of the human TNF-α receptor with the Fc portion of IgG. The protein acts to bind TNF-α and blocks the association of TNF with its receptor. It is self-injected four times a week. These drugs have proven very effective in patients with RA, and disease progression has been markedly diminished and even reversed in some instances. TNF-α also plays an important role in the body's immune responses, especially to infectious agents.

One of the **most serious adverse effects seen with the anti-TNF antibody preparations are severe infections such as tuberculosis.** These drugs should not be administered to patients who have any sign of infection. An increased risk of malignancy has also been reported in patients treated with the anti-TNF antibodies. **Neurologic problems** including dizziness, visual disturbances, and peripheral weakness have also been reported. The adverse effect profile of etanercept is similar with serious infections, neurologic disturbances, and a high frequency, 20–30 percent, of injection site reactions.

Anakinra, another DMARD, is a recombinant protein that mimics the action of IL-1Ra, a natural antagonist of the IL-1 receptor. Anakinra reduces the cartilage degradation and bone resorption caused by IL-1 in RA. **Rituximab** is a monoclonal antibody against CD-20, which is expressed mainly on B cells. It is approved for use in lymphomas and leukemias and RA. **Tocilizumab** is an anti-IL-6 receptor (IL-6R) antibody. IL-6 is an important proinflammatory cytokine and its inhibition is efficacious in RA.

Other Agents Used to Treat RA **Azathioprine** is a **cytotoxic agent that suppresses T-cell activity** to a greater extent than B-cell activity. It is an orally active agent that is metabolized to mercaptopurine, which is also **immunosuppressive.** It is

used alone or in combination with corticosteroids in the treatment of RA and other autoimmune disorders such as lupus erythematosus. Adverse effects include bone marrow suppression, leukopenia, and, less frequently, anemia. **Hydroxychloroquine** is an antimalarial agent that reduces inflammation and progression of RA. Several mechanisms have been proposed to account for this activity, including inhibition of toll-like receptors such as TLR9, increasing annexin A5 expression, and decreasing lysosomal function. Nausea and vomiting are common adverse effects and a rarely a destructive retinopathy is encountered. **Cyclophosphamide is an alkylating agent** developed as an anticancer drug. It **suppresses B-cell function** more than T-cell function. It has been used to treat a number of autoimmune disorders including Wegener granulomatosis, RA, and nephrotic syndrome in children. Its anticancer uses include non-Hodgkin lymphoma and Burkitt lymphoma. Myelosuppression, nausea and vomiting, and alopecia are common adverse reactions.

Gold salts have been used to treat patients with progressive RA who have not obtained relief from NSAIDs. Use of gold salts has diminished with the introduction of the DMARDs discussed above. Gold has a **high affinity for sulfur,** and most preparations contain gold attached to a sulfur atom.

Aurothioglucose, gold sodium thiomalate, and auranofin all contain a gold atom attached to a sulfur moiety. Gold preparations are injected IM and reach peak concentrations in 2–6 hours. Gold accumulates in organs that are rich in phagocytes and in the lysosomes of synovial cells. **Gold salts decrease the migration and the activity of macrophages,** but its precise mechanism of action is unclear. Gold salts do not have anti-inflammatory activity. The **most common adverse effects** of gold salts are **skin lesions and ulceration in mucus membranes.** Impaired **renal function** and **blood dyscrasias** are also seen in about 10 percent of patients treated with gold salts.

COMPREHENSION QUESTIONS

30.1 Infliximab is effective in RA because it does which of the following?

A. Binds to TNF-α and sequesters it from receptors
B. Is a TNF-α receptor agonist
C. Is a TNF-α receptor antagonist
D. Is a synovium-specific anti-inflammatory agent

30.2 The immunosuppressive effect of methotrexate is a result of its inhibition of which of these?

A. Dihydrofolate reductase
B. Leukocyte migration
C. Microtubule function
D. Phospholipase A_2

30.3 A 55-year-old woman is being treated for RA. Her disease has become much worse, and a new medication is added. After 6 months, she notes night sweats, weight loss, chronic cough, and a chest radiograph that indicates a cavitary lesion. Which of the following medications was most likely prescribed for the RA?

A. Gold salts
B. Infliximab
C. Methotrexate
D. Naprosyn

ANSWERS

30.1 **A.** The anti-TNF-α antibodies bind to TNF-α and prevent its association with receptors. They are not direct receptor antagonists.

30.2 **A.** Methotrexate inhibits dihydrofolate reductase, which impairs rapidly dividing cells such as lymphocytes and leukocytes.

30.3 **B.** The anti-TNF-α immunoglobulin agents are usually well tolerated and modify the disease process of RA; however, they tend to predispose patients to infections, particularly tuberculosis. The patient in the question has a typical clinical presentation of tuberculosis. Diagnosis would be confirmed by sputum culture and acid fast smear, and therapy started with multiple antituberculosis agents.

PHARMACOLOGY PEARLS

- DMARDs, with the best evidence for the anti-TNF-α agents, stop the progression of RA and may induce remission.
- Methotrexate is a folate analog that inhibits dihydrofolate reductase and acts as an immunosuppressive agent.
- Glucocorticoid agents act as immunosuppressive agents and anti-inflammatory agents but have numerous adverse effects.

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CASE 31

A 67-year-old woman is receiving chemotherapy for metastatic ovarian cancer. She is on her fourth cycle of a multidrug regimen, including cisplatin and doxorubicin. She has developed nausea and vomiting, among other side effects. You decide to premedicate her with intravenous (IV) ondansetron prior to her next dose of chemotherapy and provide oral ondansetron for home use as well.

- What is the mechanism of action of ondansetron?
- What are the common side effects associated with ondansetron?

ANSWERS TO CASE 31:
Antiemetics

Summary: A 67-year-old woman has chemotherapy-induced nausea and vomiting and is prescribed ondansetron.

- **Mechanism of action of ondansetron:** Serotonin (5-HT_3)-receptor antagonist in the central nervous system (CNS) and gastrointestinal (GI) tract.
- **Side effects of ondansetron:** Headache, diarrhea, dizziness, agitation.

CLINICAL CORRELATION

Nausea and vomiting are frequent side effects of cancer chemotherapy. Control of these symptoms is an important adjunct to chemotherapy. Several agents with varied mechanisms of action are available. The serotonin (5-HT_3) receptor system in the CNS and GI tract is felt to be a major trigger of chemotherapy-induced nausea and vomiting. Ondansetron and granisetron are specific 5-HT_3-receptor antagonists that are widely used for the treatment of this problem. Granisetron has a higher receptor affinity, is longer acting, and is more potent than ondansetron. Both drugs can be administered intravenously or orally. Metoclopramide, which is primarily a dopamine antagonist, will also antagonize the 5-HT_3 receptor when given in high doses. Metoclopramide also blocks receptors in the chemoreceptor trigger zone (CTZ) in the brain that contribute to nausea. Metoclopramide sensitizes the GI tract to acetylcholine (ACh) activity, which increases GI motility and gastric emptying. It is somewhat less effective for chemotherapy-induced vomiting than ondansetron or granisetron and has the potential for extrapyramidal side effects that are seen with dopamine antagonists.

APPROACH TO:
Pharmacology of Antiemetic Agents

OBJECTIVES

1. List the therapeutic uses of antiemetic medications.
2. Describe the mechanism of action of the antiemetic medications.
3. Describe the adverse effects of the antiemetic medications.

DEFINITIONS

Emesis: Vomiting; a complex reflex that results in forceful emptying of the contents of the stomach through the mouth and sometime the nose.

DISCUSSION

Class

Vomiting is a **complex reflex** controlled by the **vomiting center** in the **lateral reticular formation of the medulla.** The vomiting center has **five primary afferents** (see Figure 31–1):

1. The **CTZ** is located outside the blood-brain barrier and is exposed to blood-borne and cerebrospinal fluid emetogenic chemicals. Primary receptors associated with emesis are dopamine D_2, 5-HT_3, neurokinin-1 (NK_1, substance P) and opioid receptors.
2. The **vestibular apparatus** is located in the inner ear, sending afferents pertaining to motion. Primary receptors are histamine H_1 and muscarinic cholinoreceptors.
3. The **pharynx** via the vagus nerve sends afferents of the gag reflex.
4. **Enteric afferents arise** from the GI tract. 5-HT_3 receptors play an important role in these signals.
5. **Cerebral cortical afferents** with information such as stress, anticipation, psychiatric disorders.

Current antiemetic therapy blocks one or more of these afferents to reduce the activity in the vomiting center.

Serotonin 5-HT_3 Antagonists Selective 5-HT_3 antagonists are potent antiemetic agents for emetogenic signals arising in the GI tract and from the CTZ. These agents are especially useful for nausea from **chemotherapeutic agents and for postoperative- or postradiation-**induced vomiting. 5-HT_3 antagonists are not useful for motion sickness or nausea of vertigo. Four agents are currently available: **ondansetron, granisetron, palonosetron, and dolasetron.** They are all administered

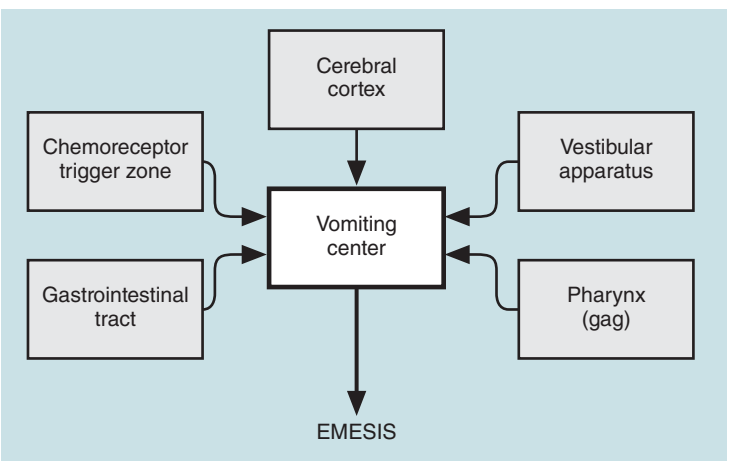

Figure 31–1. Primary afferent components to the vomiting center.

intravenously; ondansetron and dolasetron can also be administered orally. These agents are most effective if given 30 minutes prior to chemo- or radiotherapy. Oral agents may be administered once or twice daily. 5-HT_3 antagonists have been associated with QT prolongation.

NK_1 receptor antagonists, aprepitant and fosaprepitant, have made a significant improvement in the treatment of patients receiving highly emetic chemotherapy. The NK_1 antagonists are effective as sole agents and have been combined with $5HT_3$ antagonists or dexamethasone. Combination treatment is first choice for cancer-induced nausea and vomiting.

Dopamine Antagonists **Droperidol** is an **antipsychotic butyrophenone** that has significant antiemetic actions. Its antiemetic properties are mediated by **blocking dopamine receptors in the CTZ and in the vomiting center. Droperidol has been associated with a** risk of QT prolongation, ventricular tachycardia, and torsade de pointes. **Phenothiazines such as promethazine and prochlorperazine block dopamine, histamine, and muscarinic receptors** in the same regions. All are useful for treating nausea and vomiting postoperatively but are very sedating.

Extrapyramidal effects and hypotension have been reported.

Metoclopramide is a prokinetic agent that also has antiemetic actions based on its **dopaminergic antagonist activity.** It may be administered orally or parenterally for nausea following chemotherapy or for postoperative nausea. As with the other dopamine antagonists, side effects are rare but may include **extrapyramidal effects: dystonias and Parkinson syndrome** may appear days to months after treatment.

Corticosteroids **Glucocorticoids** such as dexamethasone and prednisolone are used to treat nausea and vomiting associated with **chemotherapy.** They are most frequently used in combination with other antiemetics. The molecular basis for the antiemetic action of glucocorticoids is not understood.

Antihistamines **First-generation antihistamines** such as cyclizine, diphenhydramine, and dimenhydrinate are useful to treat nausea associated with motion sickness and vertigo. They are **able to penetrate the blood-brain barrier** and their action is most likely to decrease afferents from the vestibular apparatus. The most common adverse effect of these agents is sedation.

Anticholinergic Agents **Scopolamine** is the most effective agent for treating nausea associated with **motion sickness or vertigo.** It is **not effective for nausea of chemotherapy.** It is administered via a **transdermal patch** that delivers drug at a uniform rate for up to 72 hours. By avoiding the peak levels associated with oral administration, incidence of side effects is also reduced. **Scopolamine reduces afferents from the vestibular apparatus** and **decreases the excitability of the labyrinthine receptors.** Side effects, typical of antimuscarinic agents, include **dry mouth, blurred vision, and drowsiness.** It should **not be used in patients with glaucoma or prostatic hypertrophy.**

Other Agents Used as Antiemetics **Benzodiazepines** such as lorazepam or diazepam may be used **prior to chemo- or radiotherapy** to reduce the frequency and severity of anticipatory vomiting that occurs in patients who undergo multiple

rounds of anticancer therapy. **Dronabinol** is Δ^9-tetrahydrocannabinol, the major active ingredient in marijuana. It is an orally active agent that has been used to stimulate appetite and as an antiemetic. The mechanism of these activities is not known. It is frequently administered in conjunction with a phenothiazine, which reduces the adverse effects of both agents while producing a synergistic antiemetic effect. Adverse effects include euphoria, sedation, dry mouth, and hallucinations.

COMPREHENSION QUESTIONS

31.1 A 56-year-old woman has nausea due to chemotherapy for breast cancer. Droperidol is effective in reducing nausea because it blocks which of the following?

A. ACh receptors in the periphery
B. Dopamine receptors in the CTZ
C. Glucocorticoid receptors in the vomiting center
D. 5-HT_2 receptors in the CTZ

31.2 A patient undergoing chemotherapy with cisplatin has severe nausea. Which of the following would be the drug to use in this patient?

A. Cyclizine
B. Naloxone
C. Ondansetron
D. Scopolamine

31.3 A fisherman uses a transdermal scopolamine patch to assist with the nausea associated with being on a boat. What is the most likely side effect he will experience?

A. Acute dystonic reaction
B. Euphoria
C. Sedation
D. Tremor

ANSWERS

31.1 **B.** Droperidol is a dopamine-receptor antagonist that diminishes the activity of the CTZ. It is effective in reducing nausea associated with chemotherapy or radiotherapy.

31.2 **C.** Ondansetron is a serotonin 5-HT_3-receptor antagonist with fewer side effects and greater effectiveness than the other agents in treating patients on chemotherapy.

31.3 **C.** Sedation is the most common side effect associated with scopolamine patches as a result of stimulation of the muscarinic cholinoreceptor.

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CASE 32

A 58-year-old woman with a 20-year history of poorly controlled type II diabetes mellitus comes in for routine follow-up. She has had multiple complications from her diabetes, including retinopathy and peripheral neuropathy. She complains of having several months of feeling as if her stomach is full after eating very little. She is frequently nauseous and bloated. She is on a combination of regular and neutral protamine Hagedorn (NPH) insulin for her diabetes, an angiotensin-converting enzyme (ACE) inhibitor for her blood pressure, and a statin for her lipids. Her examination today is unremarkable. A radiographic gastric emptying study shows a prolonged gastric emptying time. You diagnose her with diabetic gastroparesis and prescribe metoclopramide.

- What is the mechanism of action of metoclopramide for gastroparesis?
- What are some common side effects of metoclopramide?

ANSWERS TO CASE 32:
Prokinetic Agents

Summary: A 58-year-old woman presents with diabetic gastroparesis and is prescribed metoclopramide.

- Mechanism of action of metoclopramide: Dopamine D_2-receptor antagonist in the GI tract.
- Common side effects: Sedation, extrapyramidal side effects, increased prolactin secretion.

CLINICAL CORRELATION

Metoclopramide, administered orally or parenterally, works as a prokinetic agent in the GI tract. In the GI tract, dopamine acts to inhibit ACh stimulation of smooth muscle. As a dopamine D_2-receptor antagonist, metoclopramide allows for a greater stimulatory effect of ACh. It may also promote the release of ACh. The increased ACh effect at muscarinic receptors results in increased lower esophageal sphincter pressure and increased gastric emptying. Serotonin 5-HT_4 receptors also increase upper GI motility by direct effects as well as by increasing ACh release. Many 5-HT_4 agonists are available in other countries. Ghrelin, produced by the stomach, has important effects on gastrointestinal motility. Like motilin, a hormone released by endocrine cells in the duodenum, it induces hunger contractions in the fasting state and acts postprandially to accelerate gastric emptying. Gherlin agonists are in last phase clinical trials for treatment of gastroparesis. Diabetic gastroparesis is a common (~10%) complication of poorly controlled diabetes, particularly in diabetics with peripheral neuropathy. It is associated with damage to the vagus nerve. In this setting, metoclopramide can promote emptying of the stomach and help to alleviate the symptoms. Metoclopramide can be administered orally or parenterally and its half-life is 5 to 6 hours. It is also used clinically in combination with antacids to treat gastroesophageal reflux disease (GERD). Metoclopramide also has central actions. Dopamine D_2-receptor blockade in the CTZ in the CNS is the basis for clinical use of metoclopramide for treatment of nausea and vomiting. Restlessness, anxiety, and insomnia are common adverse effects of metoclopramide and, like other dopamine D_2-receptor antagonists such as haloperidol, metoclopramide at high doses can cause extrapyramidal side effects and tardive dyskinesia. It can also cause increased prolactin secretion that can result in galactorrhea, menstrual dysfunction, gynecomastia, and sexual dysfunction. Other prokinetic agents include erythromycin, which stimulates motilin receptors, and can be administered orally or IV for refractory gastroparesis; cisapride, a 5-HT_4-receptor agonist that is only available for compassionate use due to its cardiotoxicity; and domperidone (not available in the United States), which is also a dopamine D_2-receptor antagonist, but one that acts only peripherally and, therefore, has few neural adverse effects.

DEFINITIONS

Gastroparesis: Slight paralysis of the muscular coat of the stomach.

COMPREHENSION QUESTIONS

32.1 Metoclopramide is which of the following?

A. α_1-Adrenoceptor antagonist
B. Dopamine D_2-receptor antagonist
C. Muscarinic cholinoreceptor antagonist
D. Serotonin 5-HT_4-receptor agonist

32.2 Which of the following is the most likely adverse effect of metoclopramide?

A. Hallucinations
B. Hyperactivity
C. Hyperthyroidism
D. Tardive dyskinesia

32.3 Metoclopramide acts to achieve which of the following?

A. Increase gastric emptying
B. Decrease transit through the small intestine
C. Decrease lower esophageal sphincter pressure
D. Stimulate vomiting

ANSWERS

32.1 **B.** Metoclopramide is a dopamine D_2-receptor antagonist.

32.2 **D.** Adverse effects of metoclopramide include insomnia, tardive dyskinesia, and sexual dysfunction, as well as extrapyramidal side effects similar to haloperidol and endocrine effects related to increased prolactin secretion (galactorrhea, menstrual dysfunction, gynecomastia).

32.3 **A.** Metoclopramide increases gastric emptying, increases lower esophageal sphincter pressure, and inhibits vomiting.

PHARMACOLOGY PEARLS

- Metoclopramide works as a prokinetic agent in the GI tract, acting as a dopamine antagonist.
- Common side effects of metoclopramide are restlessness and anxiety. Also, like other dopamine D_2-receptor antagonists such as haloperidol, metoclopramide can cause extrapyramidal side effects and tardive dyskinesia.
- Metoclopramide increases prolactin secretion that can result in galactorrhea and menstrual irregularities.

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CASE 33

A 48-year-old woman presents for evaluation of abdominal pain. She reports that she gets right upper-abdominal pain after eating. It is worse if she eats fatty or fried food. She has tried over-the-counter antacids without relief. She has no significant medical history, has had no surgeries, and takes no medications on a regular basis. Both her mother and an older sister have had to have their gallbladders removed. On examination, she is moderately obese, but her examination is otherwise normal. An abdominal x-ray is normal. An ultrasound of her abdomen reveals several small gallstones. You diagnose her with cholelithiasis and recommend surgical evaluation. She is adamant in wanting to do anything to avoid surgery, so you prescribe ursodiol.

- What is the mechanism of action of ursodiol?
- How long does it take to see full effect of this medication?
- What effect does ursodiol have on low-density lipoprotein (LDL) cholesterol levels?

ANSWERS TO CASE 33:
Drugs Used to Dissolve Gallstones

Summary: A 48-year-old woman presents with cholelithiasis. She does not desire surgery, and is prescribed ursodiol.

- **Mechanism of action of ursodiol:** Reduces cholesterol secretion into bile.
- **Length of time to see full effect:** Months to years.
- **Effect on LDL cholesterol levels:** No change.

CLINICAL CORRELATION

Gallstones are a common cause of abdominal pain. These often consist of a high proportion of cholesterol, which is excreted from the liver into bile. The bile is taken up in the gallbladder, where the cholesterol may precipitate into stones. Ursodiol is ursodeoxycholic acid, a bile acid. It reduces cholesterol secretion into bile with little change in the secretion of bile acid. It is used in an effort to dissolve cholesterol gallstones in patients who either do not want surgery or are not surgical candidates. The full effect of this medication can take from several months to years. It is also used as an adjunct to shock wave lithotripsy of gallstones. In this treatment, sound waves are used to break gallstones into small fragments. Ursodiol may then be used to attempt to dissolve the fragments. Radiopaque gallstones, which contain calcium, are not effectively dissolved with ursodiol. It is administered orally, and its side effects are primarily GI, with nausea and diarrhea being common. Ursodiol does not alter LDL cholesterol levels in the blood.

APPROACH TO:
Pharmacology of Agents Used to Dissolve Gallstones

OBJECTIVES

1. Know the drugs used to dissolve gallstones and their mechanism of action.
2. Know the routes of administration and side effects of these drugs.

DEFINITIONS

Cholelithiasis: The presence of stones in the gallbladder or common bile duct, or the process of formation of such stones.

Cholecystitis: Inflammation of the gallbladder.

Lithotripsy: Reduction of gallstones, using sound waves, to small particles that can be excreted from the gallbladder.

DISCUSSION

Class

Gallstones are a major cause of morbidity and mortality, and surgical removal of the gallbladder is among the most common GI surgeries. Although surgical removal is the preferred treatment, other treatments, including **ultrasound lithotripsy** or **pharmacologic dissolution,** are therapeutic options in patients who cannot have surgery. Gallstones can be transported into the duodenum and block the exit of the pancreatic duct, causing pancreatitis. Gallstones can be radiotranslucent, indicating a stone high in cholesterol content, or **radiopaque, indicating a stone with significant mineral** (usually **calcium**) content. **Ursodeoxycholic acid (ursodiol)** is a **naturally occurring bile acid that is a minor component of bile.** It has been used **successfully to treat** relatively **small, radiotranslucent stones,** especially those within the common bile duct. It decreases the synthesis of bile and reduces the concentration of cholesterol in bile. **Ursodiol solubilizes cholesterol by forming bile acid micelles** and disperses liquid crystals of cholesterol in an aqueous environment. These actions will **slowly cause the dissolution of the gallstone.** Complete dissolution occurs in approximately 30 percent of patients with stones less than 20 mm in diameter. It also decreases the biliary colic that is associated with gallstones in some patients. The prophylactic administration of ursodiol caused a marked reduction in the incidence of gallstones after cardiac surgery. Older approaches to pharmacologic dissolution of gallstones employed organic solvents such as methyl-*tert*-butyl ether (MTBE) or monoglycerides such as monooctanoin. Although rapid dissolution of gallstones could be achieved, leakage of the solvent materials into the lumen of the bowel was associated with serious adverse effects, and these approaches have been largely discontinued. **Adverse effects of ursodiol are minor, typically GI upset and mild diarrhea.** Since bile supersaturation with cholesterol is a key factor for cholesterol gallstone formation, the lipid-lowering drug ezetimibe (see Case 13) reduces cholesterol concentration in plasma and in bile by inhibiting cholesterol secretion and may be useful in reducing the size and occurrence of gallstones.

Structure

Ursodiol is derived from 7-hydroxycholesterol and is a naturally occurring component in bile.

Administration

Ursodiol is administered orally, two to three times a day, and complete dissolution of stones may require a year. Treatment effectiveness should be monitored by diagnostic ultrasound.

COMPREHENSION QUESTIONS

33.1 Ursodiol reduces the size of common bile duct gallstones by which of the following mechanisms?

A. Chelating Ca^{2+} out of the stone
B. Decreasing the synthesis of bile
C. Increasing the cholesterol content in bile
D. Slowly dissolving cholesterol from the stone

33.2 A 35-year-old woman is noted to have cholelithiasis. She opts for medical therapy with ursodiol. Complete dissolution of a gallstone by ursodiol typically requires how long?

A. Several hours
B. Weeks
C. Months to years
D. Several years

33.3 Ursodiol has been useful to treat which of the following conditions?

A. Cholestasis of pregnancy
B. Cirrhosis
C. Diabetes mellitus
D. Pancreatitis resulting from trauma

ANSWERS

33.1 **D.** Ursodiol is a detergent that slowly causes dissolution of gallstones that are rich in cholesterol. It decreases the amount of cholesterol in bile as well as total bile acid synthesis.

33.2 **C.** Ursodiol treatment typically takes months to a year for dissolution of a typical gallstone.

33.3 **A.** Ursodeoxycholic acid has been used successfully to treat the symptoms of pruritus associated with cholestasis of pregnancy, a disease thought to be caused by the accumulation of bile salts.

PHARMACOLOGY PEARLS

- Ursodiol is the best nonsurgical therapy for small, radiotranslucent gallstones in patients who are not candidates for surgery.
- Ursodeoxycholic acid has also been used to treat cholestasis of pregnancy.

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CASE 34

A 45-year-old woman presents with bloating and "gas" after drinking milk. Her symptoms usually start approximately 2 hours after ingesting most dairy products, although she has found that yogurt with active cultures doesn't bother her much. This has been worsening over the past several years. She has learned to avoid dairy products as much as possible, but would like to be able to drink milk or eat ice cream occasionally. She has no significant medical history, takes no medications regularly, and has a normal examination. You diagnose her with lactose intolerance and suggest a trial of lactase when she plans to ingest dairy products.

- What is the cause of lactose intolerance?
- What is the mechanism of action of lactase?

ANSWERS TO CASE 34:
Enzyme Replacements

Summary: A 45-year-old woman with lactose intolerance is prescribed lactase.

- **Cause of lactose intolerance:** Insufficient production of lactase by brush border cells of the small intestine.
- **Mechanism of action of lactase:** Hydrolyzes lactose to glucose and galactose.

CLINICAL CORRELATION

Lactose intolerance is a very common digestive condition in which there is an underproduction of the natural enzyme lactase by the brush border of the small intestine. Lactase hydrolyzes lactose into the sugars glucose and galactose, which can then be transported from the lumen of the small intestine across cell membranes. A deficiency or absence of lactase results in lactose remaining within the intestinal lumen. The presence of this undigested disaccharide will osmotically attract fluid into the intestinal lumen. As it passes further into the GI tract, lactose will be metabolized by colonic bacteria, which produces bowel gas. The combination of increased amounts of fluid and gas in the intestine contributes to the symptoms of lactose intolerance. Most people with lactose intolerance learn to avoid lactose-containing foods. The low levels of endogenous lactase production in these individuals can be supplemented by lactase given orally with meals containing dairy products. This often reduces, but not completely relieves, the symptoms of gas, bloating, and diarrhea that may occur.

APPROACH TO:
Pharmacology of Enzyme Replacements

OBJECTIVES

1. Know the conditions for which digestive enzyme replacement can be used.
2. Know the specific digestive enzymes that can be replaced and the therapeutic effects of enzyme replacement.

DEFINITIONS

Pancreatin: A preparation of principally amylase, lipase, and proteases.

Pancrelipase: A preparation that is principally lipase that also contains amylase and proteases.

Gaucher disease: The most common lysosomal storage disease caused by a deficiency in **glucosylceramidase.**

Anderson-Fabry disease: A genetic deficiency of **α-galactosidase A.**

DISCUSSION

Class

Digestive enzymes hydrolyze triglycerides to fatty acids and glycerol, peptides and proteins to amino acids, and **carbohydrates to simple sugars.** Enzyme replacement is used in patients with a congenital lack of enzyme activity as a result of mutation in specific enzymes that includes exocrine pancreatitc insufficiency, lysosomal storage disease, or glycogen storage disease type 2. In addition, insufficiencies secondary to other disorders that cause deficient pancreatic exocrine secretions, such as in **cystic fibrosis, chronic pancreatitis, postpancreatectomy, pancreatic ductal obstruction, and postgastrectomy,** can be treated with enzyme replacement. Greater than 90 percent of pancreatic function must be lost before clinically significant effects on digestion are apparent: steatorrhea (from fat malabsorption) and protein malabsorption. **Sucrase** is expressed on the brush border of the small intestine primarily in the distal duodenum and jejunum. It converts sucrose into glucose and fructose. **Isomaltase and maltase** hydrolyze isomaltose and maltose, respectively, into two molecules of glucose. **Lactase** (α-galactosidase) is normally expressed in villus enterocytes in the small intestine. It breaks lactose into the monosaccharides glucose and galactose.

Pancreatic Enzyme Preparations Four FDA-approved **preparations of pancrelipase (a combination of lipase, protease, and amylase) are** currently available. These are **all prepared from porcine pancreas,** but they are not bioequivalent and are not necessarily interchangeable. These agents can prevent malabsorption from the disorders mentioned above and palliation of pain in chronic pancreatitis. Oral pancreatic enzyme replacements are well tolerated, but can cause GI disturbances such as nausea and diarrhea; allergic reactions to the porcine preparations have also been reported. Very high doses can cause hyperuricemia and hyperuricosuria, rarely fibrosing colonopathy. Pancreatic enzyme replacements are administered orally prior to a meal or snack. They are available in enteric-coated capsule or as noncoated capsules.

Small Intestine Enzyme Preparations **More than 15 percent of adults are lactose intolerant** as a result of deficiency in the enzyme lactase. This deficiency leads to **lactose delivery to the colon,** where it osmotically **traps water and it is fermented,** producing **bloating sensations,** discomfort, and intestinal gas. Preparations of lactase for enzyme replacement are prepared from the yeast *Kluyveromyces lactis*. **Lactase is administered orally,** typically taken just prior to ingestion of dairy products. The dosage may be increased until satisfactory results are obtained. Few adverse effects are reported beyond mild GI upset.

Congenital sucrase-isomaltase deficiency (CSID) is a chronic autosomal disease with highly variable levels of enzyme activity. CSID is frequently characterized by nearly complete deficiency in sucrase activity, less severe reductions in isomaltase and maltase activity, and normal lactase activity. In the absence of sucrase activity, unhydrolyzed sucrose and starch are not absorbed from the small intestine, causing osmotic water retention, loose stools, and the typical manifestations of malabsorption.

Sacrosidase is derived from baker's yeast (*Saccharomyces cerevisiae*). It is approved for use in CSID and is effective in improving carbohydrate absorption

and alleviating the GI sequelae. It is administered orally just prior to eating food. Adverse effects are rare with one case of hypersensitivity reported to date. Besides replacing enzymes in the digestive system, enzyme replacement has been useful to correct **genetic deficiencies in lysosomal enzymes. Anderson-Fabry disease** is an **X-linked lysosomal storage disease** that results from a deficiency in **α-galactosidase A.** This enzyme hydrolyses globotriaosylceramide to galactose and lactosylceramide. In patients with the enzyme deficiency, globotriaosylceramide accumulates and is deposited in vascular endothelium, smooth muscle cells, renal glomerular and epithelial cells, myocardial cells and valvular fibrocytes, and neurons. This results in severe pain as a result of damage of small neurons, as well as cardiomyopathy and renal impairment and failure. The disease can be **treated with agalsidase α,** which is a **recombinant α-galactosidase A** produced in vitro in fibroblast cells. A similar replacement enzyme is agalsidase β, which is an identical recombinant protein produced in a genetically engineered Chinese hamster ovary cell line. Both drugs are given intravenously biweekly, and both drugs reduce the globotriaosylceramide deposits and improve organ function. Both drugs are well tolerated.

Mucopolysaccharidoses (MPS) is another lysosomal storage disease caused by a deficiency in any of 11 enzymes that break down glycosaminoglycans. These lead to breakdown in connective tissues and blood elements. Currently there are enzyme replacements for the underlying enzymatic deficit in MPS I, II, and VI. **Glycogen storage disease type II (Pompe disease)** is caused by a mutation in acid alpha-glucosidase, which leads to accumulation of glycogen in heart, skeletal muscles, nerves, and liver. Alglucosidase alfa (Myozyme) is available for IV use to treat the disease at a cost of approximately $300,000/yr.

COMPREHENSION QUESTIONS

34.1 A 17-year-old patient enters your office complaining that every time he drinks a glass of milk he gets GI pain and cramping. Which of the following would be the best choice to treat his condition?

A. Aspirin
B. Lactase
C. Niacin
D. Sucrase

34.2 A 9-year-old patient whose main complaint is shooting pain in the arms and legs is seen in your hospital. After careful study you make the diagnosis of Anderson-Fabry disease. Which of the following would be the best course of treatment for this patient?

A. α-Galactosidase A
B. High-dose glucocorticoids
C. Indomethacin
D. Sacrosidase

34.3 A 45-year-old man has developed chronic pancreatitis as a result of alcohol abuse, and he has been noted to have pancreatic insufficiency. Which of the following circumstances contraindicates the use of pancreatic enzyme replacement in this patient?

A. Allergy to eggs
B. Allergy to pork
C. Diabetes mellitus
D. Pseudogout

ANSWERS

34.1 **B.** This case of lactose intolerance would be treated with lactase before consumption of dairy products.

34.2 **A.** Anderson-Fabry disease can be treated successfully with α-galactosidase A.

34.3 **B.** All pancreatic enzyme replacements are porcine and so an allergy to pork products is a contraindication.

PHARMACOLOGY PEARLS

- Enzyme replacement therapy is effective in treating specific genetic enzyme deficiencies and acquired enzyme deficiencies and is associated with very few adverse effects.
- Lactose deficiency is a common problem and is addressed by avoidance of lactose-containing products or taking lactase orally prior to ingestion of lactose.
- All pancreatic enzyme preparations currently are prepared from porcine pancreas.

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CASE 35

A 48-year-old man presents for evaluation of heartburn. He reports a burning feeling in his chest after eating. It is worse when he eats spicy foods or tomato sauce. He is sometimes awakened at night with these symptoms. He has tried over-the-counter antacids and histamine H_2 blockers with partial relief. He is on no medications regularly. His examination today is normal. An upper gastrointestinal (GI) x-ray series reveals gastroesophageal reflux. Along with appropriate diet and lifestyle modification recommendations, you prescribe omeprazole.

- What is the mechanism of action of omeprazole?
- What is the mechanism of action of antacid medications?
- What is the mechanism of action of histamine H_2-receptor antagonists?

ANSWERS TO CASE 35:
Agents for Upper GI Disorders

Summary: A 48-year-old man with gastroesophageal reflux disease (GERD) is prescribed omeprazole.

- **Mechanism of action of omeprazole:** Irreversible inhibition of the H^+, K^+-ATPase proton pump in parietal cells, reducing transport of acid from the cell into the lumen.
- **Mechanism of action of antacids:** Weak bases that directly neutralize gastric acid and reduce pepsin activity.
- **Mechanism of action of histamine H_2-receptor antagonists:** Competitive antagonists of histamine at the parietal cell histamine H_2 receptor.

CLINICAL CORRELATION

GERD, a common cause of recurrent heartburn and dyspepsia, is caused by gastric acid irritating the lining of the esophagus. It can be treated by numerous medications. Antacid medications, widely available without a prescription, usually contain aluminum hydroxide, magnesium hydroxide, calcium carbonate, or combinations thereof. They are weak bases that partially neutralize gastric acid. Histamine H_2-receptor antagonists, available over-the-counter or by prescription, competitively antagonize the effect of histamine (released from gastric mucosa enterochromaffin-like [ECL] cells) at the histamine H_2 receptor in gastric parietal cells. Omeprazole was the first medication in a class known as proton pump inhibitors (PPIs). PPIs directly and **irreversibly** inhibit the action of the H^+, K^+-ATPase that transports $H^+$from gastric parietal cells into the lumen of the stomach, thus reducing both the basal and stimulated release of gastric acid. PPIs are used for the treatment of refractory GERD, for hypersecretory conditions such as Zollinger-Ellison syndrome, for peptic ulcer disease, and as a part of the treatment regimen (in combination with antibiotics) for *Helicobacter pylori* infections. *H. pylori* is the most common cause of non-drug-induced peptic ulcer disease.

APPROACH TO:
Pharmacology of Agents for Upper GI Disorders

OBJECTIVES

1. List the antacid agents and describe their mechanisms of action, therapeutic uses, and adverse effects.
2. List the histamine H_2-receptor antagonists and PPIs that inhibit gastric acid production and describe their mechanisms of action, therapeutic uses, and adverse effects.

3. List the drugs used therapeutically to promote the defense of the GI tract from the effects of acid, and describe their mechanisms of action, therapeutic uses, and adverse effects.

DEFINITIONS

Prodrugs: Inactive compounds that are metabolized in the body to therapeutically active agents.

Proton pump: An integral membrane protein that can move H^+ across a cell membrane, mitochondria, or other organelle. Responsible for acidification of the gastric lumen.

DISCUSSION

Class

Drugs used to **treat acid-peptic diseases** (Table 35–1) either **reduce gastric acidity** (antacids, histamine H_2-receptor antagonists, and PPIs) or **promote the defense of the GI mucosa** (sucralfate, bismuth subsalicylate, and the prostaglandin analog, misoprostol).

Available **antacid preparations** are used primarily to treat heartburn and dyspepsia. When given concomitantly with other drugs, antacids may reduce their absorption through direct binding or, as a result of an increase in gastric pH, by altering their dissolution or solubility.

Available **histamine H_2-receptor antagonists** are used to treat dyspepsia, GERD, peptic ulcer disease, and stress-induced gastritis.

PPIs are generally considered the first-line drugs for treating acid peptic disease as a result of their superior efficacy and safety profile. They are significantly more effective in reducing acid secretion than H_2-receptor antagonists. All are prodrugs that must be converted to the active forms in the canalicular space. Relief of symptoms takes from 1 to 4 days. Available PPIs are also used to **treat dyspepsia, GERD, peptic ulcer disease, and stress-induced gastritis, as well as gastrinomas.** For treating peptic ulcer disease caused by ***H. pylori*, PPIs** are used in a multidrug regimen that includes the antibiotics **clarithromycin and amoxicillin and/or metronidazole.**

Sucralfate use has, for the most part, been supplanted by other agents for the treatment of upper GI disorders. It is still used clinically to treat stress-related gastritis.

Misoprostol is used to **treat nonsteroidal anti-inflammatory drug (NSAID)-induced peptic ulcer disease.**

Bismuth subsalicylate (Pepto-Bismol) is available as a nonprescription agent and is used to treat **dyspepsia, acute diarrhea,** and, as a second-line agent in a multidrug combination, ***H. pylori* infection** where it is thought to inhibit growth of the organism.

Structure

PPIs are substituted benzimidazoles. They resemble histamine H_2-receptor antagonists but have a different mechanism of action. Sucralfate is a complex salt of sucrose

Table 35–1 • MEDICATIONS FOR PEPTIC ULCERS

Antacids	**Adverse Effects**
Sodium bicarbonate	Bloating, belching, metabolic alkalosis as a result of absorbed unreacted alkali at high doses, and fluid retention caused by absorption of sodium chloride that may compromise patients with heart failure and hypertension. Hypercalcemia at high doses when administered with dairy products containing calcium.
Calcium carbonate	Bloating, belching, metabolic alkalosis, hypercalcemia.
Magnesium hydroxide	Osmotic diarrhea from unabsorbed magnesium.
Aluminum hydroxide	Constipation from unabsorbed aluminum.
Histamine H_2-Receptor Antagonist	**Adverse Effects**
Cimetidine (prototype) *Ranitidine Famotidine Nizatidine*	Mild diarrhea or constipation, headache, myalgia. Confusion, hallucinations, and excitement, particularly cimetidine, when administered IV to elderly or patients with renal or liver disease.
Proton Pump Inhibitors	**Adverse Effects**
Omeprazole (prototype) *Esomeprazole Lansoprazole Pantoprazole Rabeprazole*	Long-term use associated with osteoporosis and increased risk of fractures. Long-term use also associated with hypomagnesemia. In patients with *H. pylori,* chronic use also associated with atrophic gastritis and hyperplasia. Headache and diarrhea are minor adverse effects.
Gi Protective Agents	**Adverse Effects**
Sucralfate	Constipation as a consequence of the aluminum salt. It may bind other drugs to limit their absorption (phenytoin, quinoline antibodies).
Bismuth subsalicylate	Black stools and darkening of the tongue.
Misoprostol	Not approved for ulcer management in pregnant women although it may be used for induction of labor as a cervical ripening agent during pregnancy.

sulfate and aluminum hydroxide. Misoprostol is a prostaglandin analog of prostaglandin E_1 (PGE_1). Bismuth subsalicylate is a combination of bismuth and salicylate.

Mechanism of Action

Antacids are weak bases that directly neutralize gastric hydrochloric acid to form a salt and water and to reduce pepsin activity. They may also stimulate the production of prostaglandins and thus increase the defense of the GI mucosa. Histamine H_2-receptor antagonists are highly specific and selective competitive antagonists of histamine binding to gastric parietal cell histamine H_2 receptors. Thus they prevent activation of adenylyl cyclase and accumulation of cAMP, which mediate acid release into the gastric lumen. Parietal cell acid secretion induced by the secretagogues gastrin and acetylcholine, which act synergistically with histamine, is also inhibited by histamine H_2-receptor antagonists, albeit indirectly. PPIs irreversibly

inhibit the H^+, K^+-ATPase proton pump in parietal cells, thus reducing transport of acid from the cell into the lumen of the stomach.

Sucralfate in its viscous form may bind to positively charged proteins to coat epithelial cells and to form a physical barrier in the GI tract that protects the luminal surface and any already formed ulcers from the deleterious effects of gastric acid and pepsin.

Misoprostol, a **PGE_1 analog,** stimulates bicarbonate and mucus secretion and mucosal blood flow, resulting in enhanced neutralization and protection from secreted acid. It also binds to parietal cell prostaglandin receptors to modestly inhibit secretagogue-induced acid secretion.

Bismuth subsalicylate, like sucralfate, coats epithelial cells to form a physical barrier in the GI tract and protect it from the deleterious effects of gastric acid and pepsin. It may also stimulate bicarbonate and PGE_2 secretion.

Administration

All antacids, histamine H_2-receptor antagonists, PPIs, sucralfate, misoprostol, and bismuth subsalicylate can be given orally. The PPIs pantoprazole, esomeprazole (pediatrics), and thehistamine H_2-receptor antagonists (cimetidine, famotidine, and ranitidine) are available for parenteral use.

As over-the-counter preparations, magnesium hydroxide, which can cause diarrhea, and aluminum hydroxide, which can cause constipation, are usually administered in combination to balance their effects on the GI tract.

PPIs are inactive, acid-labile, prodrugs that are administered in acid-resistant, enteric-coated preparations to protect them from destruction in the stomach. In the acidic environment of the stomach, sucralfate forms a viscous gel.

Pharmacokinetics

The acid-neutralizing capacity of available antacid preparations varies considerably, being highly influenced by their rate of dissolution, their solubility in water, and the rate of gastric emptying among other factors. Sodium bicarbonate and calcium carbonate react more rapidly with HCl to produce CO_2 and water than do magnesium or aluminum hydroxide and, therefore, may cause bloating and belching.

Histamine H_2-receptor antagonists are absorbed rapidly; however, cimetidine, ranitidine, and famotidine have a bioavailability of only 50 percent. Their clearances can be reduced in the elderly and by renal and hepatic dysfunction. Cimetidine inhibits the activity of several hepatic cytochrome P450 enzymes that can prolong the duration of action of a number of other drugs.

PPI bioavailability is decreased significantly by food. Because maximal inhibition of H^+, K^+-ATPase occurs when proton pumps are actively secreting acid, PPIs are best administered within an hour or so of meals. After dissolution of the enteric-coated PPI capsule in the intestine, the lipophilic prodrug diffuses into the acidic environment of the parietal cell, where it becomes protonated and highly concentrated, and where it is then converted to a reactive sulfenamide cation that irreversibly binds to and inactivates parietal cell H^+, K^+-ATPase through a covalent disulfide linkage. Although their serum half-life is short (2–4 hours), PPI inhibition of the proton pump lasts up to 24 hours while synthesis of new H^+, K^+-ATPase occurs. PPIs are

metabolized by hepatic P450 microsomal enzymes; however, no clinically significant drug-drug interactions have been documented. **Sucralfate is very insoluble,** and therefore, it **acts locally** with little systemic absorption from the GI tract.

Misoprostol is absorbed rapidly and is metabolized to an active agent that has a very short serum half-life and short duration of action and therefore must be administered three to four times daily.

Bismuth subsalicylate is rapidly dissociated in the stomach into bismuth, which is eliminated in the stool, and salicylate, which is absorbed systemically.

COMPREHENSION QUESTIONS

35.1 Which of the following is the most common adverse effect of omeprazole?

A. Black stools
B. Constipation
C. Headache
D. Nausea

35.2 Ranitidine inhibits which of the following?

A. Gastrin binding to parietal cells
B. Histamine binding to parietal cells
C. H^+, K^+-ATPase
D. Parietal cell prostaglandin receptors

35.3 Which of the following is true of cimetidine?

A. It is a prostaglandin analog of PGE_1.
B. It is a prodrug.
C. It is associated with confusion and hallucinations in elderly patients.
D. It reduces the duration of action of other drugs.

ANSWERS

35.1 **D.** The most common adverse effect of omeprazole is nausea. Diarrhea, not constipation, is another common adverse effect. Black stools are associated with use of bismuth subsalicylate.

35.2 **B.** Ranitidine is a histamine H_2-receptor antagonist that inhibits histamine binding to parietal cells and reduces acid secretion. It indirectly inhibits the synergistic acid secretion stimulated by gastrin binding to parietal cell gastrin receptors. PPIs inhibit parietal cell H^+, K^+-ATPase.

35.3 **C.** Cimetidine is a histamine H_2-receptor antagonist that uniquely causes confusion and hallucinations, particularly in elderly patients. It also inhibits hepatic microsomal enzymes to increase, not decrease, the duration of action of other drugs. PPIs are prodrugs.

PHARMACOLOGY PEARLS

- Histamine H_2-receptor antagonists cross the blood-brain barrier and placenta, are secreted into breast milk, and therefore should be used judiciously during pregnancy and in nursing mothers.
- Three to four days of PPI administration is necessary to achieve maximal inhibition of acid secretion (up to 98%). Likewise, 3–4 days are needed for acid secretion to return to normal after discontinuation of therapy.
- PPIs are considered first-line agents for peptic ulcer disease and GERD.

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CASE 36

A 22-year-old man presents for the evaluation of abdominal pain and diarrhea. He states that for approximately a month he has had progressively worsening cramping pains. He has had watery diarrhea and, from time to time, has noted blood mixed in with his stool. He has lost approximately 5 lb. He has tried over-the-counter antidiarrheal medications without relief. He is on no medication regularly and has no significant medical history. Examination of his abdomen reveals it to be distended and to have hyperactive bowel sounds. It is diffusely tender with no palpable masses. Rectal examination is very painful and reveals heme-positive watery stool. A blood count shows that he has iron deficiency anemia and an erythrocyte sedimentation rate that is markedly elevated. An office sigmoidoscopy reveals changes consistent with ulcerative colitis. You start him on a short course of corticosteroids and plan to place him on long-term sulfasalazine.

- What is the mechanism of action of sulfasalazine?
- Sulfasalazine cannot be used by persons allergic to which class of antibiotics?

ANSWERS TO CASE 36:
Agents For Lower GI Disorders

Summary: A 22-year-old man with ulcerative colitis is started on a short course of corticosteroids and long-term sulfasalazine.

- **Mechanism of action of sulfasalazine:** 5-Aminosalicylic acid (5-ASA) component of sulfasalazine inhibits leukotriene and prostaglandin production in the colon.
- **Sulfasalazine cannot be used by persons allergic to:** Sulfonamides.

CLINICAL CORRELATION

Sulfasalazine is used to achieve and maintain remission in persons with inflammatory bowel disease (IBD: ulcerative colitis and Crohn disease). It is composed of two constituents—5-ASA bound by an AZO bond (N=N) to sulfapyridine. The AZO bond limits the GI absorption of the inactive, parent compound. However, in the terminal ileum and colon, bacteria break down sulfasalazine into its two components. 5-ASA is the active anti-inflammatory component. Its mechanism of action, while not entirely known, is thought to involve inhibition of the production of inflammatory leukotrienes and prostaglandins in the colon. Its activity is terminated by hepatic acetylation. Sulfapyridine, which is also acetylated, does not appear to play an active role in the reduction of inflammation in the colon. Sulfapyridine mediates the allergic cross-reaction with sulfonamide drugs. 5-ASA can also be administered as mesalamine, balsalazide, and olsalazine, which do not have a sulfa component.

Sulfasalazine, balsalazide, and olsalazine are administered orally. Mesalamine has oral, suppository, and enema formulations. The many adverse effects of sulfasalazine are due mostly to sulfapyridine, which is not well tolerated. Adverse effects are more common in slow acetylators and includes severe GI discomfort with nausea, headache, myalgia, bone marrow suppression, possible oligospermia that is reversible, and a hypersensitivity with numerous attendant serious sequelae.

APPROACH TO:
Pharmacology of Agents that Act on the Lower GI Tract

OBJECTIVES

1. List drugs used as antidiarrheal agents and describe their mechanisms of action, therapeutic uses, and adverse effects.
2. List drugs used as laxatives and describe their mechanisms of action and adverse effects.
3. List drugs used to treat irritable bowel syndrome (IBS) and IBD.

DEFINITIONS

Ulcerative colitis: Inflammatory disease of GI mucosa that is localized in the large intestine.

Crohn disease: Inflammatory disease of the GI tract that can occur anywhere from the mouth to the anus.

Irritable bowel syndrome (IBS): Recurrent abdominal pain with altered bowel movements (constipation or diarrhea), among other symptoms, that is due to alterations in motor and sensory function. This is often a diagnosis of exclusion.

Inflammatory bowel disease: Condition with symptoms of chronic GI inflammation. Includes components of increased mucosal permeability, inflammation, and visceral hypersensitivity.

DISCUSSION

Class

The agents used for **acute treatment of diarrhea of mild-to-moderate severity** (Table 36–1) may also be used for control of **chronic diarrhea** resulting from **IBD and IBS** (Table 36–2). When constipation is predominant, laxatives, particularly osmotic laxatives (eg, magnesium oxide), are used as stool softeners (Table 36–1).

Octreotide, an analog of somatostatin, is used primarily to treat diarrhea stemming from **GI tumors, AIDS, short-bowel syndrome, vagotomy, and dumping syndrome.**

Table 36–1 • ANTIDIARRHEAL AGENTS

Selected Antidiarrheal	Selected Laxatives
Opioid agonists Loperamide Diphenoxylate	*Bulk-forming laxatives* Psyllium preparations Methylcellulose Calcium polycarbophil
Kaolin	*Osmotic laxatives* Magnesium citrate Sodium phosphate Magnesium sulfate Sorbitol Lactulose PEG
Pectin	*Stool softeners* Docusate Glycerin Mineral oil
Methylcellulose resins Cholestyramine Colestipol	*Stimulant laxatives* (infrequently used) Aloe, senna, cascara, castor oil
Bismuth subsalicylate	

PEG = polyethylene glycol.

Table 36–2 • DRUGS USED TO TREAT BOWEL DISORDERS

Drugs Used to Treat IBS	Drugs Used to Treat IBD
*Alosetron	*Aminosalicylates* Sulfasalazine Balsalazide Olsalazine Mesalamine
Antispasmodic agents Calcium channel antagonists, anticholinergic agents, opioid receptor antagonists	*Glucocorticoids*
Tricyclic antidepressants Nortryptiline	*Purine analogs* Azathioprine 6-Mercaptopurine
	Methotrexate
	Anti-TNF-α agents Infliximab Certolizumab Adalimumab

*Requires physician certification and consent protocol.
IBS = irritable bowel syndrome; IBD = inflammatory bowel disease.

At low doses (50 mcg subcutaneously), octreotide is used to stimulate intestinal motility in patients with conditions that lead to intestinal obstruction or bacterial overgrowth.

Opioids Prolonged use of high doses of **diphenoxylate can result in opioid dependence.**

Kaolin-Pectin When administered concomitantly (within 2 hours of one another) **kaolins and pectins may bind other drugs in the GI tract and reduce their absorption.**

Serotonin receptor-based drugs **Alosetron** is a 5-HT_3 antagonist for severe diarrhea-predominant IBS in women only. It was removed from the market but reintroduced with strict usage guidelines. Tegaserod is a 5-HT_4 agonist for constipation-predominant IBS; it was removed from the market due to cardiovascular complication, but can be administered for compassionate use with strict guidelines.

Methylcellulose Resins **Cholestyramine and colestipol** may cause **bloating and constipation** and in some patients may result in insufficient absorption of fat. Like kaolinpectin, the use of **octreotide** may result in constipation and abdominal pain.

The formation of gallstones resulting from reduced gallbladder contractility, and the development of hyperglycemia, and sometime hypoglycemia, as a consequence of an imbalance in the secretions of insulin, glucagons, and growth hormone may also occur with octreotide therapy. **Reduced pancreatic secretions may result in steatorrhea and deficiency of fat-soluble vitamins.**

Anti-TNF-α drugs

Infliximab, adalimumab, and certolizumab are currently used for induction and maintenance therapy in patients who have moderately to severely active UC or Chron's disease with an inadequate response to aminosalicylates or corticosteroids. Other anti-TNF-α agents and biologic therapies are undergoing evaluation in clinical trials for their efficacy in IBD.

Bulk-Forming and Osmotic Laxatives **Bulk-forming and osmotic laxatives** (except PEG) can cause flatulence and bloating. Osmotic laxatives can result in electrolyte imbalance and should be used cautiously in patients with renal insufficiency or cardiac dysfunction. PEG is used to cleanse the colon prior to endoscopy. If aspirated, mineral oil can cause severe lipid pneumonia and when used chronically can result in decreased fat-soluble vitamin absorption.

Structure

Kaolin is a naturally occurring hydrated magnesium aluminum silicate, whereas pectin is derived from apples. Octreotide is a more stable, biologically active octapeptide analog of the 14-amino acid regulatory peptide, somatostatin.

PEG is an osmotically active sugar.

Mechanism of Action

Kaolin and **pectin absorb fluids as well as bacteria** and other toxic agents in the GI tract.

The **opioids, loperamide, and diphenoxylate inhibit** the **release of acetylcholine** from cholinergic nerves in the submucosa and myenteric complex to disrupt coordinated colonic motility and to increase water absorption and transit time through the GI tract.

Cholestyramine and colestipol bind excess diarrhea-causing bile salts that may accumulate in Crohn disease or from resection of the terminal ileum where bile salts are normally absorbed.

Octreotide, like somatostatin, **inhibits the release of numerous GI hormones** (eg, gastrin, cholecystokinin, serotonin) that results in decreased intestinal fluid secretion and, depending on the subcutaneous dose, increased (50 mcg) or decreased (100–250 mcg) motility among many other effects, including reduced pancreatic secretions.

Bulk-forming laxatives, which are not absorbed from the GI tract, absorb water to form a gel or increase the fluidity of the stools that distends the colon and induces peristalsis. Osmotic laxatives, which are also not absorbed from the GI tract, increase the fluidity of stools. Stool softeners increase the penetration of water and lipids into compacted fecal material (docusate, glycerin) or coat it (mineral oil) to prevent the loss of water.

Administration

Loperamide, administered orally, is a nonprescription opioid agonist. Diphenoxylate is administered orally in combination with low doses of atropine (which also may contribute to the antidiarrheal activity of the preparation) to preclude its self-administration as a drug of abuse.

Octreotide can be administered intravenously or subcutaneously and in a subcutaneous depot formulation. All laxatives are administered orally except glycerin, which is administered rectally as a suppository. PEG is administered with an isotonic balanced salt solution to prevent the development of intravascular fluid or electrolyte imbalance.

All of the anti-TNF-α are administered by infusion or injection.

Pharmacokinetics

Commercial preparations of kaolin and pectin are not absorbed from the GI tract. Loperamide does not cross the blood-brain barrier and therefore has no analgesic activity or, importantly, potential for abuse that limits the use of other opioids as antidiarrheal agents.

Diphenoxylate, although very insoluble, does penetrate the central nervous system (CNS), and therefore, its continuous use can result in opioid dependence.

Octreotide has a serum half-life of 90 minutes, compared with somatostatin, which has a serum half-life of approximately 3 minutes. Its duration of action can be extended up to 12 hours by subcutaneous administration and up to a month by using a depot formulation.

Sorbitol and lactulose are metabolized by colonic bacteria.

COMPREHENSION QUESTIONS

36.1 Which of the following drugs crosses the blood-brain barrier?

A. Diphenoxylate
B. Kaolin
C. Loperamide
D. Methylcellulose

36.2 Which of the following drugs inhibits the release of acetylcholine from cholinergic nerves in the submucosa and myenteric complex?

A. Cholestyramine
B. Docusate
C. Loperamide
D. Pectin

36.3 Which of the following drugs shows an allergic cross-reaction with an antibiotic?

A. Diphenoxylate
B. Octreotide
C. Psyllium
D. Sulfasalazine

ANSWERS

36.1 **A.** Diphenoxylate can cross the blood-brain barrier and cause dependence. Methylcellulose and kaolin are not absorbed from the GI tract. Loperamide does not cross the blood-brain barrier.

36.2 **C.** The opioid loperamide inhibits release of acetylcholine from cholinergic nerves in the submucosa and myenteric complex to disrupt coordinated colonic motility and to increase water absorption and transit time through the GI tract. Pectin absorbs fluids in the gastrointestinal tract. Stool softeners like docusate increase the penetration of water and lipids into compacted fecal material.

36.3 **D.** Sulfasalazine is composed of 5-ASA and sulfapyridine. Sulfapyridine, which does not appear to play an active role in the reduction of inflammation in the colon, mediates an allergic cross-reaction with sulfonamide drugs.

PHARMACOLOGY PEARLS

- Antidiarrheal agents should not be used to treat patients experiencing bloody stools or high fever because of the increased risk of aggravating the underlying condition.
- Cholestyramine and colestipol bind excess diarrhea-causing bile salts.
- IBS is a diagnosis of exclusion and requires a thorough medical workup.
- Many laxatives are commonly overused by the lay public.

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CASE 37

An 8-year-old boy is brought to your office because of a chronic cough. His mother says that he coughs frequently throughout the day and will have symptoms 2 or 3 nights a month as well. This has been a problem on and off for approximately a year, but seems to be worse in the spring and fall. He also coughs more when he is riding his bike or playing soccer. He has been treated twice in the past year for "bronchitis" with antibiotics and cough suppressants but he never seems to clear up completely. His examination is normal except for his lungs, which reveal expiratory wheezing. You diagnose him with asthma and prescribe an albuterol inhaler.

- What is the mechanism of action of albuterol?
- What are the most common side effects of albuterol?
- What medications can be used to provide long-term control of the asthma symptoms?

ANSWERS TO CASE 37:
Agents Used to Treat Asthma

Summary: An 8-year-old boy with asthma is prescribed an albuterol inhaler.

- **Mechanism of action of albuterol:** β_2-Adrenoreceptor agonist in bronchial smooth muscle causes smooth muscle relaxation, inhibits the release of mediators from mast cells, and stimulates mucociliary clearance.
- **Most common side effects of albuterol:** Skeletal muscle tremor, tachycardia, and cough.
- **Medications for the long-term control of asthma:** Inhaled corticosteroids, long-acting β_2-adrenoreceptor agonist, cromolyn, or nedocromil; second-line agents include oral theophylline, leukotriene inhibitors, or systemic corticosteroids.

CLINICAL CORRELATION

Asthma is a disease of chronic airway inflammation. This inflammation can cause episodes of wheezing, coughing, and breathlessness, which are reversible either spontaneously or with treatment. The inflammation can also increase bronchial reactivity to certain stimuli, such as allergens, infectious agents, or exercise, which may trigger bronchospasm and symptoms. Inhaled β_2-adrenoreceptor agonists (β-agonists) are widely used to treat the acute bronchospastic episodes. They work to relax bronchial smooth muscle via a cyclic adenosine monophosphate (cAMP)-mediated reduction in intracellular calcium concentrations, resulting in relaxation. The increase in cAMP also reduces the release of mediators from mast cells in the airways. Frequent use of these agents can result in a tachyphylaxis. Patients who require frequent dosing with inhaled β-agonists should also be treated with medications to reduce the frequency of bronchospastic events. These include inhaled corticosteroids, long-acting β-agonists, cromolyn or nedocromil, and oral methylxanthines, corticosteroids, or leukotriene modifiers. Inhaled β-agonists commonly cause tremor, tachycardia, and cough.

APPROACH TO:
Pharmacology of Drugs Used to Treat Asthma

OBJECTIVES

1. Understand the medications used in the treatment of asthma, their mechanisms of action, and adverse effects.
2. Know the difference between short-acting symptomatic treatments and long-acting preventive therapies.
3. List the mediators of airway inflammation involved in asthma.

DEFINITIONS

Bronchoconstriction: Constriction of the bronchial air passages, as a result of increased tone in airway smooth muscle cells.

Tachyphylaxis: Decreasing response to a drug with repeated dosing.

DISCUSSION

Class

Asthma is characterized by **acute episodes of bronchoconstriction** caused by **underlying airway inflammation.** A common finding in asthmatics is **an increased responsiveness** of the **bronchi and trachea** to **exogenous or endogenous stimuli** that results in **inappropriate contraction of smooth muscle in the airway,** and production of **thick viscid mucus** and **mucosal thickening from edema and cellular infiltration.** Asthma typically occurs with both an **early-phase response** lasting approximately 1 to 2 hours that is triggered by autocoids and inflammatory mediators such as **histamine, leukotrienes, and prostaglandins.** Immunoglobulin E-sensitized (IgE-sensitized) mast cells play a key role in the early-phase response. The late-phase response that occurs 2 to 8 hours later is mediated by cytokines from T-helper type 2 (Th2) lymphocytes including granulocyte-macrophage colony-stimulating factor (GM-CSF), and interleukins 4, 5, 9, and 13. These mediators attract and activate eosinophils and increase IgE production by B cells. This leads to the chronic bronchoconstriction, continued mucus production, and cellular infiltration that typify the underlying inflammation in asthma.

There are currently **six classes of drugs** used to treat asthma: **β-adrenoreceptor agonists, acetylcholine antagonists, glucocorticoids, leukotriene modifiers, chromones,** and **anti-IgE monoclonal antibodies.** The National Asthma Education and Prevention Program has revised its 1997 guidelines on the treatment of asthma as illustrated in Table 37–1.

Table 37–1 • RECOMMENDATIONS FOR PHARMACOLOGIC MANAGEMENT OF ASTHMA IN ADULTS AND CHILDREN OLDER THAN 5

Asthma Severity	Symptom Frequency	Medications
Mild intermittent	<2 days/week, <2 nights/month	No regular therapy; short-acting β_2-agonists as needed for symptom relief
Mild persistent	>2 per week but <once per day >2 nights/month	Low-dose inhaled glucocorticoids. Alternate: cromolyn, nedocromil, leukotriene modifier, *or* sustained release theophylline
Moderate persistent	Daily, >1 night/week	Low- to medium-dose glucocorticoids and long-acting inhaled β_2-agonists. Alternate: leukotriene modifier or theophylline
Severe persistent	Continual during day, frequent at night	High-dose glucocorticoids *and* long-acting inhaled β_2-agonist *and* (if needed) systemic glucocorticoids. Consider omalizumab for allergy sufferers

The recommendation for quick relief in all patients regardless of severity is two to four puffs of a **short-acting inhaled β_2-agonist one to three times per occurrence.** Use of short-acting β_2-agonists more than two times a week may indicate the need to initiate long-term therapy. Short-acting β_2-selective drugs for use in asthma include albuterol, levalbuterol, terbutaline, metaproterenol, and pirbuterol. These agents bind specifically to the β_2-adrenergic receptor and avoid the cardiovascular effects of β_1-activation. Activation of β_2-receptors causes bronchodilation. Onset of action occurs in minutes and lasts for 4–6 hours. Albuterol and terbutaline can be administered orally; terbutaline is available for subcutaneous injection for emergency treatment. Few side effects of short-term use of β_2-agonists have been reported. With regular use these agents can cause transient hypokalemia, which manifests as muscle cramping. Excessive use of the oral preparations may result in cardiovascular effects such as tachycardia.

Long-acting inhaled β_2-agonists, such as salmeterol and formoterol, have a much longer half-life (up to 12 hours). These agents are available in metered-dose inhalers that produce fewer side effects than systemic administration. Use of long-acting agents produces the same relaxation in airway smooth muscles and also appears to decrease the release of mediators from mast cells and lymphocytes. The long-acting agents should not be used to reverse an acute attack. Long-acting β_2-agonists may induce tolerance to albuterol, thus limiting their efficacy in acute exacerbations, which possibly increases mortality. The FDA has a black box warning for this class of drugs, which cites an increased risk of asthma exacerbation and asthma-related death. These drugs should never be prescribed as monotherapy.

Glucocorticoids are an important treatment for **mild persistent and more severe asthma.** Glucocorticoids are **potent anti-inflammatory agents** that reduce the production of inflammatory mediators, cause apoptosis of leukocytes, and decrease vascular permeability. They **do not cause relaxation of bronchial smooth muscle.** The glucocorticoids are used for the prophylactic treatment of asthma; they have no appreciable effect on an acute event. Glucocorticoids administered by **inhalation** provide a high concentration of drug where needed and **minimizes the amount in the systemic circulation.** However, some drug is swallowed during inhalation and some drug is absorbed into the systemic circulation through the lung. Adverse effects are attributable to local effects of the glucocorticoids or the drug entering the systemic circulation. These include **oral candidiasis, increased loss of calcium from bone,** and rarely, **suppression** of the **hypothalamic-pituitary-adrenal axis. Systemic use of glucocorticoids** is recommended in patients with **severe persistent asthma** (see Table 37–1).

Leukotrienes B_4, C_4, and D_4 play an important role in the pathogenesis of asthma. LCB_4 is a potent neutrophile chemoattractant, and LTC_4 and LTD_4 are involved in bronchoconstriction and overproduction of airway mucus. These mediators are derived from arachidonic acid via the enzyme 5-lipoxygenase. Two classes of drugs have been developed that interfere with leukotrienes. **Zileuton** is an **inhibitor of 5-lipoxygenase** and thereby **decreases the biosynthesis of leukotrienes. Zafirlukast** and **montelukast** are **specific, competitive, Cys-LT1 receptor antagonists.** The **Cys-LT1** receptor is responsible for **mediating the bronchoconstrictor activity of all leukotrienes.** The two classes of drugs are equally **effective in the treatment**

of mild-to-moderate persistent asthma and appear to be about **as effective as low-dose inhaled glucocorticoids.** All of the leukotriene modifiers are administered orally; the receptor antagonists may be taken once or twice a day. Zileuton is taken four times a day and is associated with **liver toxicity;** therefore, **monitoring liver enzymes is recommended.**

The **methylxanthines** include theophylline, theobromine, and caffeine; theophylline is used as a **second-line agent to treat asthma.** Theophylline was originally thought to act by **inhibiting cyclic nucleotide phosphodiesterases,** thereby **increasing intracellular cAMP and cyclic guanosine monophosphate (cGMP).** Theophylline is also an **antagonist of adenosine receptors,** and this mechanism of action might be especially important in asthma because **activation of pulmonary adenosine receptors results in bronchoconstriction.** However, the precise mechanism of action of theophylline in the lung remains controversial. Theophylline produces **bronchodilation** and improves long-term control of asthma. Theophylline is available for oral administration, as a suppository, and for parenteral use. Plasma levels of theophylline show considerable variability between patients, and the drug has a **narrow therapeutic window;** blood levels need to be monitored. Infants and neonates have the slowest rates of clearance.

The **chromones, cromolyn and nedocromil,** are unique drugs used for the **prophylaxis** of **mild-to-moderate persistent asthma.** A variety of mechanisms of action have been proposed for these agents including inhibition of mediator release from mast cells and suppression of activation of leukocytes. These various effects are now thought to be mediated by **inhibition of various chloride channels that are responsible for secretion and cellular activation.** They have **no effect on airway smooth muscle tone** and are **ineffective in reversing bronchospasm;** thus they are truly for prevention. Both agents are administered by inhalation and are effective in reducing both antigen and exercise-induced asthma. They are poorly absorbed into the systemic circulation and have mild adverse effects including throat irritation, cough, and nasal congestion. More serious adverse reactions including anaphylaxis, anemia, and pulmonary infiltration are rare.

Inhaled acetylcholine muscarinic cholinoreceptor antagonists have a use in treatment of asthma, but they have been somewhat superseded by other agents. Muscarinic antagonists can effectively block the bronchoconstriction, and the increase in mucus secretion that occurs in response to vagal discharge. **Ipratropium bromide** is a **quaternary ammonium derivative of atropine** that can be administered by inhalation that is **poorly absorbed into the systemic circulation.** Ipratropium bromide causes variable degrees of **bronchodilation** in patients; this may reflect the variable degree that parasympathetic stimulation contributes to asthma in individual patients. Ipratropium bromide is useful in patients that are unresponsive or cannot tolerate β_2-receptor agonists and in chronic obstruction pulmonary disease. In addition, ipratropium bromide increases the bronchodilator activity of albuterol in the treatment of severe acute attacks.

IgE bound to mast cells plays an important role in antigen-induced asthma. **Omalizumab**, a **monoclonal antibody that targets circulating IgE** and prevents its interaction with mast cells, is approved for the treatment of asthma, specifically in patients whose allergies exacerbate asthma. By decreasing the amount of IgE

antibodies available to bind mast cells, IgE cross-linking is less likely and subsequently, the mast cell release of those mediators is decreased. In clinical trials, **omalizumab significantly reduced IgE levels** and reduced the magnitude of both the early- and late-phase responses to antigen. **Omalizumab is indicated for adults and children older than 12 years with moderate-to-severe persistent asthma** who have a **positive skin test or in vitro reactivity to a perennial aeroallergen** and whose **symptoms are inadequately controlled with inhaled corticosteroids.** It is available only as a subcutaneous injection. The **most frequent adverse events include injection site reaction, viral infections, upper respiratory tract infection (20%), sinusitis, headache, and pharyngitis.** These events are observed at similar rates in omalizumab-treated patients and control patients. More serious adverse effects include malignancy (0.5%) and anaphylaxis.

Administration

For both inhaled steroids and inhaled β_2 agonists, delivery of medication is crucial. When using a metered dose inhaler (MDI), the use of a spacer will dramatically increase the amount of medication delivered. Many trials have shown that using a spacer + inhaler is equal or better than a nebulizer for delivery.

COMPREHENSION QUESTIONS

37.1 Zileuton is effective in treating asthma because it performs which of the following?

A. Antagonizes leukotriene receptors
B. Inhibits cyclooxygenase
C. Inhibits 5-lipoxygenase
D. Inhibits mast cell degranulation

37.2 A 19-year-old woman has a history of asthma for 10 years, and complains of an acute onset of wheezing. Which of the following drugs would be best for treatment of an acute attack of asthma?

A. Inhaled albuterol
B. Oral albuterol
C. Oral dexamethasone
D. Oral salmeterol

37.3 A 21-year-old woman with moderately severe asthma on three-drug treatment has elevated liver function tests thought to be caused by one of her medications. Which drug is causing this adverse effect?

A. Chromone agent
B. Leukotriene receptor antagonist
C. Lipoxygenase inhibitor
D. Methylxanthines

37.4 A 25-year-old man has bronchospasm that is exercise induced, particularly in the cold weather. He takes his medication 15 minutes prior to anticipated exercise, which will help to prevent the asthmatic attack but does not produce bronchodilation. Which drug does he take?

A. β-Agonist inhaler
B. Chromone agent
C. Glucocorticoid inhaler
D. IgE inhibitor

37.5 A 16-year-old female with severe persistent asthma is placed on multiple medications. She has been taking her medications as instructed, but one of the medications is causing her to have tachycardia, nausea, and jitteriness. She has been informed of the need to measure serum levels of this medication. Which medication is the source of the undesirable side effects?

A. Anticholinergic inhaler
B. Leukotriene receptor antagonist
C. Lipoxygenase inhibitor
D. Methylxanthines

ANSWERS

37.1 **C.** Zileuton diminishes the production of leukotrienes by inhibiting 5-lipoxygenase.

37.2 **A.** Inhaled albuterol would provide the fastest acting and most localized therapy for an acute attack.

37.3 **C. Zileuton** is an inhibitor of 5-lipoxygenase, and thereby decreases the biosynthesis of leukotrienes; it is associated with liver toxicity.

37.4 **B.** Chromones are prophylactic agents, useful especially for exercise or cold-induced bronchospasm.

37.5 **D.** The methylxanthine agents have a low therapeutic index and often can cause adverse effects.

PHARMACOLOGY PEARLS

- Inhaled corticosteroids are the treatment of choice for the long-term management of persistent asthma.
- Use of short-acting β_2-agonists more than twice weekly indicates inadequate control, and examination of long-term treatment should be considered.
- Long-acting β_2-agonist should always be used in conjunction with an inhaled corticosteroid.

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CASE 38

A 32-year-old woman comes to your office during the height of the spring pollen season complaining of sneezing and congestion. She gets these symptoms every year. Her nose runs constantly, her eyes water and itch, and she sneezes. She is only getting partial relief from oral antihistamines. She asks if there is anything else that she can do for her allergies. On examination she has red, irritated conjunctiva with clear eye drainage and periorbital discoloration ("allergic shiners"). Her nasal mucosa is boggy and appears congested. You agree with her diagnosis of seasonal allergic rhinitis and prescribe a corticosteroid nasal spray to be used along with her oral antihistamine.

- How long does it take to see the full effect of nasal steroids?
- What are the common side effects of nasal steroids?

ANSWERS TO CASE 38:
Rhinitis and Cough Medications

Summary: A 32-year-old woman with seasonal allergic rhinitis is prescribed nasal steroid medication to take together with her antihistamine.

- **Length of time until maximal effect of nasal steroids:** 1–2 weeks.
- **Common side effects:** Nasal burning, throat irritation, nose bleeds.

CLINICAL CORRELATION

The mechanism of action of nasal steroids for allergic rhinitis is not entirely Known; however, it does reduce allergic inflammation by downregulating the transcription and activity of cytokines. Corticosteroids have a wide range of activity on many inflammatory mediators, including histamine, cytokines and leukotrienes, and cell types such as mast cells, eosinophils, and macrophages, which are involved in allergic symptoms. Nasal steroids are effective at reducing the congestion, rhinitis, and sneezing associated with seasonal and environmental allergies. They require treatment for up to 2 weeks before maximal benefit is seen. For that reason it is recommended that they be used on a daily, not an as needed, basis. The adverse effects of nasal steroids are primarily a result of local effects, because they are not largely systemically absorbed. These include nasal burning and bleeding and throat irritation.

Histamine (H_1-receptor) antagonists are also widely used for allergic rhinitis and may be used in combination with nasal steroid medications. Antihistamines alone are less effective than nasal steroids. H_1-receptors are membrane bound and coupled to G-proteins. Their activation leads to increased phospholipase C activity, with increases in diacylglycerol and intracellular Ca^{2+}. The net effect of this in blood vessels is vasodilation and increased permeability, which clinically contributes to the mucosal swelling and congestion seen in allergic rhinitis. The H_1-receptor antagonists, therefore, cause vasoconstriction and decreased permeability, thereby decreasing these symptoms.

APPROACH TO:
Pharmacology of Drugs Used to Treat Rhinitis and Cough

OBJECTIVES

1. Understand the characteristics of rhinitis and cough.
2. List the drugs used for rhinitis, their mechanisms of action, and adverse effects.
3. Know the agents used to treat cough, their mechanisms of action, and adverse effects.

DEFINITIONS

Rhinitis: Inflammation of the mucus membranes of the nose.

Allergic conjunctivitis: An inflammatory condition of the conjunctiva secondary to an allergic stimulus. Common symptoms include itchy, red, and tearing eyes.

DISCUSSION

Class

Rhinitis is caused by **increased mucus production, vasodilation, and increased fluid accumulation in mucosal spaces. Inflammatory mediators** including **histamine, leukotrienes, interleukins, prostaglandins, and kinins** are responsible for these effects. Increased production of these mediators can be provoked by an allergic response, or a bacterial or viral infection.

Allergic rhinitis affects 20 percent of the adult population and up to 40 percent of children. **The hallmark of allergic rhinitis is an IgE-mediated inflammatory response.** Antihistamines, anticholinergics, intranasal corticosteroids, and chromones have proven to be useful in treating allergic rhinitis.

Both **first- and second-generation histamine H_1-receptor blockers** (see Case 24) are useful in treating **acute allergic rhinitis,** but their long-term benefits are questionable. First-generation agents, including diphenhydramine, cyclizine, and chlorpheniramine, have been shown to reduce sneezing, nasal congestion, and nasal itching. Second-generation agents, including fexofenadine, cetirizine, and loratadine, have comparable efficacy and significantly fewer adverse effects such as sedation and dry mouth. Second-generation antihistamines effectively reduce all seasonal allergic rhinitis symptoms in children, but dosages must be appropriately reduced. Following oral administration, effects are seen with antihistamines in 1–2 hours. The most common adverse effects seen with the second-generation agents are headache, back pain, and cough.

Inhaled nasal corticosteroids such as beclomethasone, budesonide, flunisolide, fluticasone, and triamcinolone acetonide are **useful for long-term management of allergic rhinitis.** This **route of administration reduces the frequent adverse effects associated with systemic administration of corticosteroids.** Corticosteroids are potent anti-inflammatory agents and reduce both the production of inflammatory mediators (cytokines, leukotrienes, and prostaglandins) and cellular components (mast cells, eosinophils, basophils, lymphocytes, macrophages, and neutrophils). The major adverse effects seen with inhaled corticosteroids are **pharyngitis and an increased risk of upper respiratory tract infections.**

The **chromones,** cromolyn and nedocromil, have also been used to treat allergic rhinitis. These agents are administered by inhalation and are poorly absorbed into the systemic circulation. Their major action is to reduce the activity of a number of chloride channels that are important in the release of mediators such as histamine. The major adverse effects of these agents are bronchospasm, cough, and nasal congestion (which can be severe); less frequent adverse effects include anaphylaxis, dizziness, and anemia.

Nasal decongestants are α-adrenoreceptor agonists that **reduce the discomfort** of allergic rhinitis, and to a lesser extent congestion associated with the common cold or flu, by decreasing the volume of nasal mucosa and **causing vasoconstriction of capacitance vessels in the nasal passages.** The most common α-adrenergic agent used as a decongestant is **pseudoephedrine** (a stereoisomer of ephedrine), which acts directly on **α_1-adrenoreceptors.** Because of the potential for psuedoephedrine to be converted into methamphetamine, it is being replaced by the slightly less effect phenylephrine. Ephedrine has largely been discontinued as a decongestant because it has significant central nervous system (CNS) effects. A major limitation in the use of these agents is rebound hyperemia and worsening of symptoms that often occurs with chronic use or after discontinuation. **Oxymetazoline** is an inhaled adrenergic agonist that can be used for no more than 3 days to alleviate nasal congestion. Nasal decongestants should be used with caution in patients with hypertension.

The leukotriene receptor antagonist, **montelukast**, is an oral agent that also is effective in the treatment of allergic rhinitis.

Cough and Antitussives Cough is produced by the cough reflex, which is integrated in the cough center in the medulla. The initial stimulus for cough arises in the bronchi where irritation causes bronchoconstriction. Stretch receptors in the trachea and bronchial tree monitor the state of this bronchoconstriction and send vagal afferents to the cough center that trigger the cough reflex. Agents that have antitussive activity act either to relieve the bronchoconstriction or reduce the activity of the cough center.

Codeine and hydrocodone are opioid congeners that are used as antitussives. Cough suppression occurs at lower doses than required for analgesia. The exact mechanism of the antitussive activity of the opioids is unclear because isomers devoid of binding to classic receptors still display antitussive activity. Both codeine and hydrocodone are available as syrups for oral administration.

Dextromethorphan is the d-isomer of the codeine analog methorphan. It is the most common antitussive agent prescribed. It has no analgesic or addictive properties and does not act through the classic opioid receptors. Binding sites for dextromethorphan have been identified in membrane preparations from various parts of the brain, but it is still unclear whether they mediate the antitussive actions of the drug.

β-Adrenergic agonists have been shown to reduce cough without having any significant central effects. This **action is likely mediated within the bronchi** and reduces vagal afferent signals to the cough center.

Benzonoate is a tertracaine congener that acts peripherally as an anesthetic on respiratory stretch receptors to achieve its antitussive effects. **Guaifenesin** is an expectorant that stimulates respiratory tract secretions, thereby decreasing mucus viscosity.

COMPREHENSION QUESTIONS

38.1 Pseudoephedrine is used to treat nasal congestion because of which of the following?

A. It is an α_1-adrenergic agonist.
B. It is an α_2-adrenergic agonist.
C. It inhibits leukotrienes.
D. It inhibits the production of IgE.

38.2 A 34-year-old man complains of nasal congestion and a "runny nose." Which of the following would be the best for long-term management of a patient with allergic rhinitis?

A. Diphenhydramine
B. Inhaled glucocorticoids
C. Oral glucocorticoids
D. Oral pseudoephedrine

38.3 A 24-year-old man is taking two medications to help with the symptoms of allergic rhinitis. He is noted to have a blood pressure of 150/70 mm Hg. The clinician notes that one of the medications may be responsible for the new-onset hypertension. The most likely etiology is which of the following?

A. Inhaled chromone
B. Inhaled glucocorticoids
C. Oral diphenhydramine
D. Oral pseudoephedrine

ANSWERS

38.1 **A.** Pseudoephedrine is the most common agent used today as a decongestant. It is a directly acting α_1-sympathomimetic agent.

38.2 **B.** Systemic glucocorticoids cause too many adverse effects; pseudoephedrine acts primarily only on nasal congestion; diphenhydramine is not useful for long-term management.

38.3 **D.** Pseudoephedrine has activity on the α_1-adrenergic receptor, causing vasoconstriction to the nasal mucosa. Hypertension may also be seen at times.

PHARMACOLOGY PEARLS

- The hallmark of allergic rhinitis is an IgE-mediated inflammatory response.
- Antihistamines are useful for treating symptoms of acute rhinitis, but their long-term benefit is questionable.
- Pseudoephedrine has activity on the α_1-adrenergic receptor, causing vasoconstriction to the nasal mucosa.

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CASE 39

A 67-year-old man complains of pain in his right hip for the past few weeks. He has had no injury to the area and describes the pain as a "bone ache" that does not radiate. Review of systems is positive only for some weakness of urinary stream and having to get up twice a night to go to the bathroom. His general physical examination is normal. His hip examination is normal with a full range of motion and no tenderness. Examination of his prostate reveals it to be firm, enlarged, and nodular. Blood tests show a markedly elevated prostate-specific antigen (PSA), and biopsy of the prostate shows carcinoma. A bone scan confirms the presence of metastatic disease in the right hip. Along with other adjuvant therapies, a decision is made to start depot leuprolide acetate.

- Leuprolide acetate is an analog of which hypothalamic hormone?
- What is the mechanism of action of leuprolide acetate?
- Which pituitary hormones are affected by leuprolide acetate, and how are they affected?

ANSWERS TO CASE 39:

Drugs Active on the Hypothalamus and Pituitary Gland

Summary: A 67-year-old man with metastatic prostate cancer is to receive depot leuprolide acetate.

- **Leuprolide acetate is an analog of which hypothalamic hormone:** Gonadotropin-releasing hormone (GnRH).
- **Mechanism of action of leuprolide acetate:** Chronic administration of GnRH analog results in the reduction of the number of GnRH receptors in the pituitary (downregulation), with resultant decreases in pituitary gonadotropin production.
- **Pituitary hormones affected:** Luteinizing hormone (LH) and follicle-stimulating hormone (FSH) production is reduced.

CLINICAL CORRELATION

The hypothalamic-pituitary-gonadal axis is a classic example of a hormonal stimulation-negative feedback system. The hypothalamus produces GnRH, which binds to specific receptors on pituitary gonadotropic cells. These cells then produce LH and FSH, which act on the gonads. LH and FSH regulate the female menstrual cycle by their effects on the ovarian follicles and the ovarian production of estrogen and progesterone. In males, LH and FSH regulate spermatogenesis and the production of testosterone in the testes. Estrogen, progesterone, and testosterone then function as feedback signals for the hypothalamic production of GnRH. Leuprolide acetate is a synthetic 9-amino acid analog of GnRH. When initially administered, leuprolide acetate results in increases in LH, FSH, and gonadal steroid production because of its action as a GnRH agonist. However, with chronic administration, there is a reduction in the number of GnRH receptors in the pituitary gonadotropic cells. This causes a reduction in FSH or LH production and a resultant reduction in gonadal hormone production. In women this effect may be beneficial in conditions such as endometriosis, where estrogen stimulates the growth and activity of the ectopic endometrial tissue, which causes symptoms. The effect in men is to lower the production of testosterone to near castrate levels. Because prostate cancer is often testosterone dependent, leuprolide acetate can be used as a treatment for prostate cancer in those who are not surgical candidates, do not desire surgery, or have metastatic disease. Leuprolide acetate must be administered parenterally, and it has a depot form which is active for up to 3 months. It commonly causes "menopausal" side effects, such as hot flashes, as a result of the reduction in gonadal hormone production. Other antiandrogenic drugs such as abiraterone, which blocks the conversion of pregnenolone to androgens by inhibiting CYP17, can be used in combination with leuprolide or as sole therapeutic agents.

APPROACH TO:

Pharmacology of Neuroendocrine Drugs

OBJECTIVES

1. Understand the receptors and second messengers involved in the endocrine system.
2. Understand the hypothalamic-pituitary axis and its feedback system.
3. Know the drugs used as agonists and antagonists on the hypothalamic-pituitary axis, their therapeutic uses, mechanisms of action, and adverse effects.

DEFINITIONS

Prostate cancer: Common malignancy in men that may be confined to the prostate gland or metastasize to pelvic lymph nodes or bone.

Hormonal therapy: Various malignancies are sensitive to hormones, and thus medications that act as agonists or antagonists are used for therapy.

DISCUSSION

Class of Agents

The **hypothalamic-hypophyseal-end organ system** is a classic negative feedback pathway (Figure 39–1). The multiple steps in this regulatory pathway, and both positive and negative regulation, provide several targets for pharmacologic intervention. The **hypothalamus** secretes a number of **releasing factors,** including **GnRH, corticotropin-releasing hormone (CRH), thyrotropin-releasing hormone (TRH), and growth hormone-releasing hormone (GHRH),** that are of clinical significance.

These neuroendocrine factors are secreted by the hypothalamus into the hypothalamic-hypophyseal portal circulation, and they act on cognate cell types within the pituitary and cause an increase in the secretion of specific pituitary hormones. For example, **GnRH** produces an increase in the synthesis and release of both **gonadotropins, LH and FSH.** This action is mediated by a specific **seven-transmembrane G-protein-coupled receptor** that binds GnRH in cells called gonadotrophs.

FSH acts on the **ovary** to cause **follicular development and maturation; LH** causes an increase in the production of **estradiol** and is required for maintenance of the **corpus luteum.** The **LH surge** at midmenstrual cycle triggers **ovulation.** In men, **FSH is required for spermatogenesis, and LH causes an increase in testosterone production.** The actions of the two gonadotropins are also mediated by specific G-protein-coupled receptors in the ovary and testis.

17β-Estradiol and testosterone are released into the circulation, and these sex hormones have effects on many tissues. Predominantly **estradiol in women,** and **testosterone and estradiol in men** (produced by peripheral conversion of testosterone to estradiol), act on the hypothalamus and pituitary to decrease the production of the releasing hormone and the gonadotropins, respectively. This closes the negative feedback loop. As in all target tissues, the estrogen and testosterone receptors in the

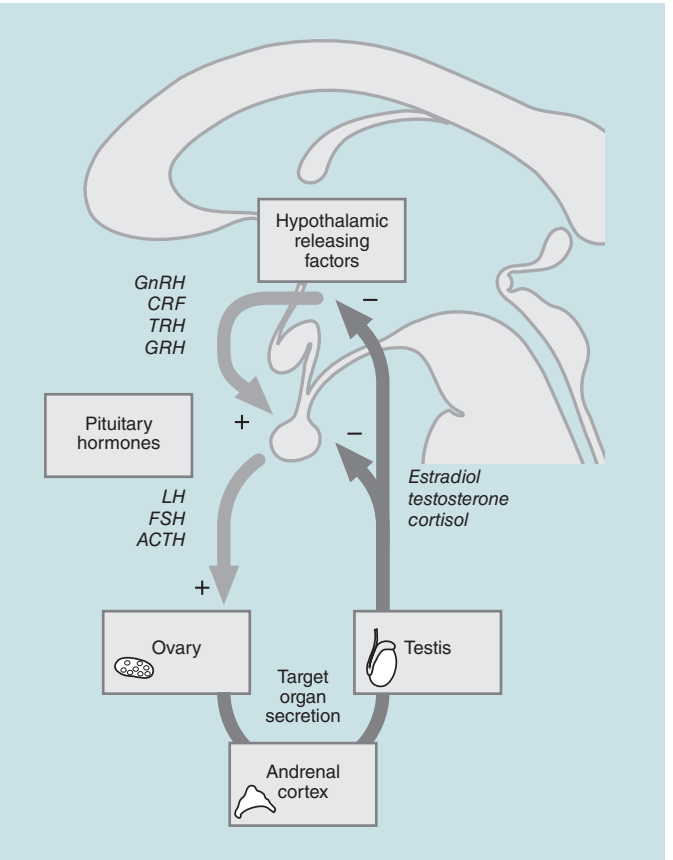

Figure 39–1. Interaction among the hypothalamus, pituitary, and gonad. GnRH = gonadotropin-releasing hormone; CRH = corticotropin-releasing hormone; TRH = thyrotropin-releasing hormone; GHRH = growth hormone-releasing hormone; LH = luteinizing hormone; FSH = follicle-stimulating hormone; ACTH = adrenocorticotropic hormone.

pituitary and hypothalamus are nuclear receptors that modulate the transcription of target genes.

The **adrenal cortex** is regulated in a similar manner. **Corticotropin-releasing factor (CRF)** is released **from the hypothalamus,** and it elicits the synthesis and release of **adrenocorticotropic hormone (ACTH)** from the **pituitary. ACTH acts on the adrenal cortex** and causes an increase in the synthesis of **cortisol from the zona fasciculata** and **adrenal androgens from the zona reticularis.**

The secretion of **growth hormone by the pituitary** is regulated in a different manner. Growth hormone secretion is stimulated by the **hypothalamic hormone GHRH** and is **inhibited by somatostatin.** Somatostatin acts in a number of tissues besides the pituitary; it inhibits the release of glucagon and insulin from the pancreas and inhibits the secretion of a number of gut peptides. **Prolactin** secretion from the pituitary is also controlled by **positive and negative regulatory factors.** The

most important pharmacologically is the **prolactin-inhibitory factor (PIF) activity of dopamine agonists.**

APPROACH TO:

Pharmacologic Uses of Hypothalamic Peptides and Analogs

Leuprolide acetate and gonadorelin acetate are synthetic peptide GnRH analogs that are administered either by subcutaneous injection, as a long-acting implant, or by IV infusion. Nafarelin acetate is a comparable peptide analog that can be administered by nasal spray. The frequency of administration is critical to the therapeutic goal. **Acute or pulsatile administration of GnRH analogs increases** production of **LH and FSH** by the pituitary. Used in this manner, GnRH analogs are useful to **stimulate spermatogenesis and testosterone production in men, and to induce ovulation or treat primary hypothalamic amenorrhea in women. Chronic administration,** for example, daily injections or use of depot preparations, **decreases** the production of FSH and LH by the pituitary. This is caused by a **depression in the number of GnRH receptors on gonadotrophs. Chronic leuprolide administration** can be used to achieve maximum androgen blockade (MAB), which **reduces testosterone production by the testis** that is **therapeutically equivalent to orchiectomy.** In men, this is useful to control androgen-dependent hyperproliferation as in **advanced prostate cancer and prostatic hyperplasia.** In women, chronic leuprolide leads to markedly diminished estrogen production, which is useful in treating a number of estrogen-dependent hyperproliferative diseases. These include **endometriosis, polycystic ovary disease, and uterine leiomyomas.** Chronic leuprolide has also been used to treat hirsutism in women. The major adverse effect in women is a chemical menopause with vasomotor symptoms and the potential for osteoporosis. In men, leuprolide has been associated with the flare phenomenon, increased cancer growth as a result of transient increase in testosterone production on initiation of therapy. Other adverse effects in men include hot flashes, gynecomastia, and testicular atrophy. A new class of pure GnRH antagonists, including cetrorelix and ganirelix, have been approved for treatment of infertility. These agents do not cause the initial agonist activity seen with leuprolide. Their main advantage is a reduction in the required days of fertility drug therapy per cycle from several weeks (ie, 3 weeks) to several days. These agents are not yet approved for use in men.

Somatostatin is unique among the hypothalamic peptides because of its widespread *inhibitory* activity on secretion and cellular proliferation. **Octreotide** is an 8-amino acid cyclopeptide with potent somatostatin agonist activity. Its action to decrease secretion of serotonin, gastrin, vasoactive intestinal peptide, secretin, motilin, and pancreatic polypeptide makes it useful to treat hypersecretory states such as VIPomas, chronic pancreatitis, and watery diarrhea from a number of causes including AIDS. Its antiproliferative uses include colorectal cancer and leukemia, and diabetic retinopathy. It is in clinical trials for additional malignancies. It has also been used to treat acute portal hypertension. It is approved for use in the treatment of acromegaly. Adverse effects include nausea, cramps, and increased gallstone formation.

Other hypothalamic peptides are used primarily as diagnostic agents. **GHRH** is a 40-amino acid peptide that can be administered IV for the diagnostic evaluation of idiopathic growth hormone deficiency. Similarly, IV administration of **TRH** is useful in the differential diagnosis of thyroid diseases. **CRH** is a 41-amino acid polypeptide found in the hypothalamus and the gut. CRH is used in cases of ACTH deficiency to distinguish between hypothalamic-pituitary or primary adrenal disease.

The **PIF** activity of **bromocriptine** or **levodopa** can be used to treat states of prolactin excess as in some cases of amenorrhea, galactorrhea, and prolactin-secreting tumors.

COMPREHENSION QUESTIONS

39.1 Which of the following best describes the action of somatostatin?

A. Inhibition of growth hormone release
B. Inhibition of prolactin release
C. Stimulation of insulin release
D. Stimulation of LH release

39.2 In the first 2 weeks following a single injection of leuprolide in a man, one would expect which of the following?

A. Decreased LH production
B. Decreased testosterone production
C. Increased LH receptors
D. Increased testosterone production

39.3 A 22-year-old woman has severe endometriosis with dysmenorrhea. She is treated with depot leuprolide acetate. One week after her first injection, she notes a marked increase in the dysmenorrhea. What is the explanation?

A. Direct effect of leuprolide on the endometrial implants
B. Likely flare with increased gonadotropin effect prior to downregulation of receptors
C. Probable placebo effect
D. Resistance of her endometriosis to the leuprolide and probable need for another agent

ANSWERS

39.1 **A.** Somatostatin is a major regulator of growth hormone, and its effect is inhibitory of growth hormone release.

39.2 **D.** Acute leuprolide will increase FSH/LH and sex steroid production and have little effect on receptor numbers.

39.3 **B.** The initial response to GnRH analog is an increase in FSH and estrogen, leading to an exacerbation of the endometriosis. Thereafter, there is a down-regulation of GnRH receptors of the pituitary, leading to a decrease in FSH and estrogen.

PHARMACOLOGY PEARLS

- The frequency of administration of leuprolide determines its effect:
- Acute administration will increase FSH/LH and sex steroids, and chronic administration will decrease FSH/LH and sex steroids.
- Chronic leuprolide administration leads to androgen blockade in men, which is useful in treating hormone-dependent cancers such as prostatic carcinoma.

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CASE 40

A 28-year-old woman presents for an evaluation of infertility. She and her husband have been attempting to conceive unsuccessfully for a year. She has never been pregnant. She has a history of irregular menstrual cycles, which were treated with oral contraceptive pills for 5 years. She has not taken contraceptives in the past 3 years. She has no other medical history, she takes no medications, and there is no family history of infertility. She does not smoke cigarettes or drink alcohol. Her routine physical and gynecologic examinations are normal. Blood tests were also normal. Basal body temperature charts that she brings in with her show no midcycle temperature elevation, and home urine ovulation prediction tests have all been negative. Her husband has already seen his physician, had a normal examination, and has had a normal semen analysis. She is diagnosed with infertility secondary to anovulation and started on clomiphene citrate.

- What is the mechanism of action of clomiphene?
- How does clomiphene induce ovulation?

ANSWERS TO CASE 40:
Drugs Active on the Gonadal and Reproductive System

Summary: A 28-year-old woman with infertility and anovulation is treated with clomiphene citrate.

- **Mechanism of action of clomiphene:** Weak partial agonist of estrogen receptor in most tissues.
- **Mechanism of induction of ovulation:** Inhibition of estrogen feedback on hypothalamus and pituitary with resultant increase in FSH, which induces follicle production in the ovaries and ovulation.

CLINICAL CORRELATION

The menstrual cycle is regulated by the hypothalamic-pituitary-ovarian axis. GnRH produced in the hypothalamus stimulates the pituitary hormones FSH and LH, which induce the maturation of follicles and release of ova from the ovaries. Estrogen and progesterone produced in the ovaries create a feedback loop on the hypothalamus and pituitary. Clomiphene is a competitive antagonist of the estrogen receptor. It is used for the treatment of infertility in women who have anovulatory menstrual cycles. By antagonizing estrogen receptors in the pituitary gland, clomiphene disrupts the normal negative feedback on the release of FSH. The elevated levels of FSH then help to induce the development of follicles in the ovaries. Potential risks of the use of clomiphene include the stimulation of multiple follicles and release of multiple eggs, with a resultant multiple gestations. It may also cause ovarian enlargement. The antiestrogen effect may precipitate hot flashes and abnormal uterine bleeding.

APPROACH TO:
Pharmacology of Gonadal Steroids and their Antagonists

OBJECTIVES

1. Understand the structures, mechanism of action, and effects of natural gonadal hormones.
2. Know the therapeutic uses and adverse effects of estrogens, progestins, and androgens.
3. List the types, uses, and adverse effects of hormonal contraceptives.
4. Describe the drugs used as antiestrogens, antiprogestins, and antiandrogens, their therapeutic uses, mechanisms of action, and adverse effects.

DEFINITIONS

Nuclear receptor: A superfamily of receptor molecules that are activated by steroid hormones, fatty acid derivatives, or products of metabolism such as bile acids. They act by altering the rate of transcription of specific target genes.

ERE: Estrogen-response element. A DNA sequence motif that binds estrogen receptors. The consensus sequence is GGTCANNNTGACC.

PRE: Progesterone-response element. A DNA sequence motif that interacts with progesterone A or progesterone B receptors.

SERM: Selective estrogen receptor modulator. A group of drugs that display tissue-specific estrogen agonist or antagonist activity.

DISCUSSION

Class

Estrogens and Progestins The **gonadotropins and sex steroids** comprise a collection of drugs that have a number of uses including **infertility, contraception, hormone replacement, osteoporosis, and cancer. Antagonists** acting within the system also have uses in treating **hormone-dependent cancers and as abortifacients.** The **menstrual cycle** is controlled by a complex feedback system between the hypothalamus, pituitary, and ovaries (see Case 39). LH and FSH are released from the pituitary on stimulation by GnRH released from the hypothalamus. **GnRH is released from the hypothalamus in a pulsatile manner under the control of the "pulse generator" in neurons in the arcuate nucleus.** In the proliferative phase of the menstrual cycle, the pulse generator causes release of GnRH at a rate of approximately one pulse per hour, and consequently **release of LH and FSH** from the pituitary is also **pulsatile.** The **intermittent release of GnRH is a key to controlling the menstrual cycle** because continuous infusion of GnRH results in cessation of release of the pituitary gonadotropins, estrogen, and progesterone, and produces amenorrhea. FSH acts on the graafian follicle to cause maturation of ova and the secretion of estrogen. As estrogen levels rise, LH and FSH production is inhibited because of negative feedback that diminishes the *amplitude* of the GnRH pulse; release of FSH is also diminished by inhibin that is released by the ovary. At midcycle, alterations in the responsiveness of the pituitary to gonadotropins occur, and the negative feedback pattern is replaced by a period of positive feedback when estradiol causes an increase in the release of LH and FSH. This change in pituitary responsiveness requires levels of serum estradiol above 150 pg/mL for 36 hours. The positive feedback elicits the midcycle surge of LH and FSH that causes ovulation. After ovulation, the corpus luteum is able to secrete progesterone for its lifetime of 14 days if pregnancy does not occur. Progesterone decreases the frequency of the hypothalamic pulse-generator and inhibits LH and FSH release from the pituitary. A frequent cause of infertility is a disruption in the complex feedback regulatory patterns that results in anovulation.

The **ovary produces a number of estrogens;** the most important are **17β-estradiol and estrone.** 17β-Estradiol and estrone are classical steroid hormones containing a four-ring structure and 18 carbon atoms. **Progesterone** is also a classical steroid composed of **21 carbon atoms.**

The effects of estrogen and progesterone are mediated by **hormone-specific nuclear receptors.** There are **two types of estrogen receptors,** termed ER_α and ER_β. Most tissues express more ER_α, but the relative amount of the two receptors is tissue and cell dependent. The precise role that each of these receptors plays in mediating the various effects of the estrogens is unclear. 17β-Estradiol has the highest affinity for the ERs; estrone binds to both receptors with a lower affinity than estradiol. ER_α and ER_β are nuclear receptors that reside within the nucleus bound to the promoters of target genes at estrogen response elements even in the absence of ligand. On binding an estrogen, a conformational change occurs in the receptor such that additional proteins are recruited to the receptor. These proteins, called coactivators, are able to increase the transcription rate of estrogen-dependent target genes. There are also two forms of the progesterone receptor called PRA and PRB. These two isoforms are derived from a single gene by differential use of two promoters within the progesterone receptor gene. Human PRB contains an additional 164 amino acids on the amino terminus of the mature protein; the rest of the PRB is identical to PRA. Both receptors reside within the nucleus bound to PREs and activate gene expression in a fashion similar to ERs, but the target genes are different as a result of differences in the sequence of ERE compared to PRE. In most circumstances, PRA inhibits the action of PRB (and of some other nuclear receptors such as ER_α and ER_β as well). Thus, the amplitude of the effects elicited by progesterone depends on the ratio of the two isoforms.

Estrogens and progesterone have a variety of pharmacologic uses including oral contraception, hormone replacement therapy (HRT) in postmenopausal women, treatment of osteoporosis, and for failure of ovarian development.

Oral Contraceptives **Oral combination contraceptives** contain **synthetic estrogens,** most commonly **ethinyl estradiol,** and a **progestin** (for example, norethindrone or norgestrel). Over the past several years the doses of estrogen in combination oral contraceptives have diminished, and the ratio of estrogen to progestin has evolved from a fixed ratio (monophasic) to biphasic and triphasic regimens with varying ratios that attempt to more closely mimic the ratio during the normal menstrual cycle. **The primary mechanism of action of oral contraceptives is prevention of ovulation.** The midcycle LH surge is absent, and endogenous estrogen levels are reduced. Oral contraceptives also alter transport of the ovum down the fallopian tube; increase the viscosity of mucus produced by the cervix, which impairs sperm entry; and create an endometrial environment less favorable to implantation. Several preparations are available for continuous dosing for 84 or 365 days; this reduces the number of bleeding periods per year.

Progestin-only contraceptives may be administered as a daily oral dose, a **depot injection** (medroxyprogesterone acetate), or as a **progestin** (L-norgestrel) **implant.** Their effectiveness approaches combination oral contraceptives, and both the depot injection and the implants have the advantage of a long duration of action (14 weeks for the injection, 5 years for the implants). Progestins alone inhibit ovulation approximately 70 percent of the time, but their effectiveness is increased by effects on the endometrium and cervical mucus production.

Several emergency ("morning-after") contraceptive regimens have been used effectively to prevent pregnancy if used within 72 hours of coitus. The most common

regimen consists of 2 combination oral contraceptive pills containing 50 mcg of ethinyl estradiol and 500 mcg of norgestrel or levonorgestrel immediately and 2 at 12 hours. Alternative (Plan B) schedule includes 2 doses of 750 mcg of L-norgestrel over 1 day; Plan B One Step is one 1.5 mg dose of L-norgestrel.

Hormone Replacement Therapy The decline in the production of estrogens that occurs at and following menopause is associated with **increased rates of bone loss** that can result in frank **osteoporosis, vasomotor symptoms** such as hot flashes and night sweats, vaginal dryness and thinning, and genital atrophy. All of these symptoms can be **alleviated by estrogens,** but careful assessment of the risk-benefit ratio for a given patient is essential. The most commonly prescribed oral estrogen preparation for postmenopausal therapy is a complex mixture of natural estrogens (conjugated equine estrogen, Premarin), by mass mostly estrone sulphate and equilin estrogens, and this is usually combined with medroxyprogesterone acetate to avoid unopposed estrogenic stimulation of the endometrium. Other HRT or estrogen replacement therapy (ERT) regimens include oral esterified estrogens, micronized estradiol, and transdermal delivery of estradiol.

Other Uses of Estrogens and Progestins Estrogens can be used to treat circumstances of inadequate hormone production as in **primary hypogonadism.** This treatment is usually begun early (ages 11–13) to facilitate the development of the secondary sexual organs and to stimulate maximal growth.

Estrogens are also useful in the treatment of **intractable dysmenorrhea** where inhibition of ovulation may be of therapeutic value. Relatively high doses of estrogens have been used to suppress ovarian production of androgens. Both of these therapeutic approaches depend on estrogen-mediated negative feedback inhibition of gonadotropin release.

Estrogen/progesterone combinations as in oral contraceptives can also be used to reduce acne, to regulate menstrual cycles, to diminish menstrual flow, and for preventing or improving menstrual migraines. IV estrogen is also used in gynecology for symptomatic menorrhagia in the acute setting.

Adverse Effects of Estrogens and Progestins Most of the adverse effects associated with estrogens and progestins are extensions of their physiologic actions. **Uterine bleeding** is the most common adverse effect associated with use of estradiol. The **increased risk of cancer** caused by estrogen and progesterone use remains a significant concern. **Unopposed estrogen treatment** has been well documented to cause an approximate threefold increase in the risk of **endometrial cancer.** Addition of a progestin to a treatment regimen essentially eliminates this increased risk. Several very large clinical trials examining use of estrogens to treat postmenopausal women have indicated that there is an **increased risk of breast cancer with estrogen** plus progesterone treatment, and further studies suggest that it is the progestin that is likely responsible for this effect. The absolute number of breast cancers that might be attributable to the HRT was very low and appears to be confined to the 60- to 69-year-old cohort. These studies do also show that estrogens *decrease* the risk of endometrial, ovarian, and colon cancer. The net effect of estrogens and progestins on cancer remains unresolved.

Despite their action to improve serum lipid levels (decreasing low-density lipoprotein [LDL] cholesterol and increasing high-density lipoprotein [HDL] cholesterol), and despite a history of anecdotal evidence, data are accumulating that the **most common HRT (Premarin or Prempro) does not reduce the risk of cardiovascular disease in older (60–69 years old) people.** The interpretation of these data has been vigorously debated, but it now appears that HRT may be protective in women in the 50- to 59-year-old cohort who did not experience a long, estrogen-free period. Estrogens do increase the risk of stroke; the underlying mechanism for this increased risk is unclear, but may involve the increased coagulability that is associated with estrogen treatment. Estrogens increase the synthesis of fibrin and coagulation factors II, VII, VIII, IX, and X, and decrease the concentration of antithrombin III. In addition, plasminogen activator inhibitor activity is increased. These changes all contribute to a heightened tendency to form blood clots. This mechanism may also participate in the increased risk of dementia in postmenopausal women treated with estrogens. It must be noted that these serious adverse effects have been documented only with Premarin or Premarin plus progesterone at a fixed dosage, and it is not certain if other dosing regimens or other estrogen preparations cause similar untoward effects. Less serious adverse effects of estrogens include nausea and vomiting and peripheral edema. Some women complain of severe migraine when taking estrogens.

Antiestrogens and SERMs **Fulvestrant** is a **pure antiestrogen** that **antagonizes** the action of estrogen in all tissues examined. Clomiphene is a partial agonist that consists of two isomers, *cis*-clomiphene and *trans*-clomiphene. *Cis*-clomiphene is a weak estrogen agonist, whereas *trans*-clomiphene is a potent estrogen antagonist. **Clomiphene binds to both ER_α and ER_β, and blocks estrogen activation of these receptors.** The major pharmacologic action of clomiphene is to **block estrogen-mediated negative feedback in the pituitary.** This increases the amplitude of LH and FSH pulses and induces ovulation in women with amenorrhea, Stein-Leventhal syndrome, and dysfunctional bleeding with anovulatory cycles. It does increase the number of ova released, thereby increasing the chances of twinning.

Fulvestrant is a 7α-alkylamide derivative of estradiol that binds to both **ER_α and ER_β.** It is administered as a depot injection. The predominant action of fulvestrant is to increase the degradation of ER_α while having little effect on ER_β. This alteration in the ratio of ER_α/ER_β may explain its usefulness in women with tamoxifen-resistant breast cancer. **Adverse effects of the antiestrogens include hot flashes, ovarian enlargement, and nausea.**

The **SERMs,** tamoxifen, raloxifene, and toremifene, are a class of compounds that display a range of agonist to antagonist activities in a tissue-specific manner. For example, tamoxifen is an estrogen receptor antagonist in the breast but is a weak estrogen agonist in the endometrium. The basis for this tissue specificity is a combination of drug-induced conformational changes in the receptor, and the complement of coactivators expressed in a given cell type. As noted above, when estradiol binds to an ER, a conformational change occurs that facilitates an interaction between coactivator proteins and ER. The SERMs also bind to ER, but they induce a conformation that is different from that caused by estradiol. The configuration of the receptor dictates which coactivator can bind to the receptor; if a cell does not express a coactivator that can bind to the receptor, then the effect of drug

binding will be antagonism in that cell type. If the cell does express a coactivator that recognizes a particular configuration, then the drug will have agonist (or partial agonist) activity.

Tamoxifen is a triphenylethylene, is structurally related to diethylstilbestrol, and binds to both ER_α and ER_β. It acts as an **estrogen antagonist in the breast and in the brain,** but it has **weak estrogen agonist activity in the uterus and in bone.** It has mixed action in the liver, decreasing total cholesterol and LDL cholesterol but with no effect on triglycerides. **Tamoxifen is highly efficacious in the treatment of breast cancer in ER positive tumors.** Tamoxifen has been shown consistently to increase disease-free survival and overall survival; treatment for 5 years has reduced cancer recurrence by approximately 50 percent and death by nearly 30 percent. It is approved for primary prevention of breast cancer in women at high risk, where it causes a 50 percent decrease in the incidence of invasive breast cancer and a 50 percent reduction of noninvasive breast cancer. Because of the development of drug-resistant tumors, treatment should last for no more than 5 years. Adverse effects of tamoxifen include hot flashes, nausea, and vaginal bleeding.

Toremifene also is a triphenylethylene with a chlorine substitution. It is also used for the treatment and prophylaxis of breast cancer.

Raloxifene is a polyhydroxylated nonsteroidal compound with a benzothiophene core. Raloxifene binds with high affinity for both ER_α and ER_β. Raloxifene is an **estrogen agonist in bone**, where it exerts an antiresorptive effect. It reduces total cholesterol and LDL cholesterol. Raloxifene **does not have agonist activity in the uterus.** Its **primary use is the prevention of osteoporosis** in postmenopausal women. Adverse effects include **hot flashes, deep vein thrombosis,** and cramps in the lower extremities.

Aromatase inhibitors include exemestane, anastrazole, and letrozole. These agents act by reducing the peripheral conversion of precursors such as androstenedione and testosterone into estrogens. They significantly suppress serum estradiol levels and offer an alternative to tamoxifen in postmenopausal women with receptor-positive breast cancer.

Antiprogestins **Mifepristone** (RU-486) is a 19-nor steroid that has both antiprogestational and antiglucocorticoid effects. It is used most commonly as an **abortifacient in the first trimester** of pregnancy. A single oral dose of mifepristone combined with a vaginal suppository containing prostaglandin E_1 is effective in terminating pregnancy in approximately 95 percent of cases if used in the first 7 weeks of gestation. Adverse effects include nausea, vomiting, and abdominal cramping.

Androgens and Antiandrogens **Testosterone** produced by the testes is the major androgen in humans. In many peripheral tissues, testosterone is converted to dihydrotestosterone by the enzyme 5α-reductase. Most circulating testosterone is bound in the plasma to sex-steroid binding globulin (SSBG). Testicular production of testosterone is regulated by LH released from the pituitary in a manner similar to that of estrogen as previously described. Testosterone has two physiologic actions. As an anabolic agent it promotes linear bone growth and development of internal genitalia, and increases muscle mass. As an androgenic agent, it is responsible for the development of male secondary sexual characteristics. **Dihydrotestosterone** is responsible

for the development of external genitalia and hair follicle growth during puberty. Testosterone or dihydrotestosterone binds with high affinity to the androgen receptor (AR), another member of the nuclear receptor family of transcription factors.

There are two distinct chemical classes of androgens: **testosterone and its esters** and the **17-alkyl androgens.** Testosterone esters include testosterone enanthate, testosterone cypionate, and testosterone undecanoate. The 17-alkyl androgens include methyltestosterone, oxandrolone, danazol, and stanozolol. Testosterone and its esters are administered either as depot injections via transdermal patch or as a gel. The 17-alkyl androgens are orally active.

The **major use of the androgens is the treatment of male hypogonadism,** both in adults and in prepubertal boys who produce low amounts of testosterone. Use in adults has been reported to increase libido, reduce senescence, and reduce the rate of bone resorption. The **major adverse effects of testosterone** and its esters are caused by the **androgenic actions,** which are especially apparent in women and prepubertal children. In women, these adverse effects include hirsutism, acne, amenorrhea, and a thickening of the vocal chords. In **children, androgens can cause premature closure of the epiphyses.** In men, androgens can produce azoospermia, decreased testicle size, and prostatic hyperplasia. The major adverse effects of the 17-alkyl androgens include masculinization and also serious hepatotoxicity. A cholestatic jaundice that is reversible on discontinuation of drug may occur.

Antiandrogens Abnormal growth of the prostate is usually dependent on androgenic stimulation. This hormonal stimulation can be reduced by orchidectomy or high doses of estrogens, but either of these treatments may be undesirable. **Chemical orchiectomy** can be accomplished with an inhibitor of GnRH synthesis such as **leuprolide** or with **antiandrogens.**

Finasteride and dutasteride are steroid derivatives that competitively inhibit 5α-reductase type II. Because **prostate growth is dependent on DHT rather than testosterone,** blockade of the enzyme can reduce stimulation of the gland. In clinical trials, finasteride decreased the incidence of prostate cancers but may have led to more aggressive tumors. **Abiraterone** is a potent inhibitor of CYP17 and thereby blocks the metabolism of pregnenolone to androgens. It is effective in the treatment of metastatic castrate-resistant prostate cancer. **Bicalutamide and nilutamide are moderately potent antiandrogens** that antagonize AR. These drugs are usually combined with a GnRH analog such as leuprolide to decrease LH and subsequently testosterone production. **Flutamide is an AR antagonist** that blocks the action of testosterone in target organs. It has been used in the treatment of prostatic carcinoma.

COMPREHENSION QUESTIONS

40.1 Clomiphene acts to induce ovulation by which of the following mechanisms?

A. Diminishing ER-mediated negative feedback at the pituitary
B. Increasing the action of ER_α in the hypothalamus
C. Increasing the action of ER_α in the ovary
D. Increasing the amount of ER_α

40.2 Progesterone is added to estrogens in HRT to achieve which of the following effects?

A. Decrease the estrogen action on the breast

B. Decrease the occurrence of endometrial cancers

C. Increase the effectiveness of the estrogens

D. Inhibit bone resorption

40.3 A 55-year-old woman is noted to be taking tamoxifen to help with breast cancer. She also complains of vaginal bleeding. She asks why she is having vaginal bleeding if the medication blocks estrogen effect in the body. Which of the following is the best explanation?

A. It has estrogen agonist effect of the breast and uterus, thereby leading to endometrial hyperplasia.

B. It is an estrogen antagonist in the breast and uterus, leading to loss of endometrial cells.

C. It has an antagonist effect on the breast but an agonist effect on the uterus.

D. It has no effect on the uterus, and the vaginal bleeding is caused by something else.

ANSWERS

40.1 **A.** Clomiphene decreases estradiol's negative feedback in the pituitary, and this increases the amplitude of the LH pulse that is responsible for ovulation.

40.2 **B.** Progestins are added to HRT regimens to decrease the risk of endometrial cancer.

40.3 **C.** Tamoxifen has an estrogen antagonist effect on the breast but a weak agonist effect on the uterus, leading to endometrial hyperplasia in some women. Endometrial cancer is seen in some patients.

PHARMACOLOGY PEARLS

- Clomiphene is the agent of choice for treatment of infertility as a result of anovulation in women with an intact hypothalamic-pituitary-ovarian axis.
- SERMs are tissue-specific estrogen antagonists that have uses in the treatment of breast cancer and osteoporosis.
- Antiandrogens are used to treat androgen-dependent cancers such as prostate carcinoma.

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CASE 41

A 45-year-old man presents for the evaluation of weight gain. He has noticed a 20-lb weight gain in the past few months without any change in his diet or activity level. He has started developing "stretch marks" on his abdomen as well. His wife has noted that even his face seems to be "growing fatter." Review of systems is significant for complaints of fatigue, multiple recent upper respiratory infections, and the development of facial acne. He has no significant medical history and takes no medications. There is a family history of diabetes and hypertension. On examination, his blood pressure is elevated at 165/95 mm Hg, but his other vital signs are normal. His face is plethoric, and he has a small fatty hump developing on his upper back. His abdomen is obese but soft and nontender without masses or fluid. Skin examination is notable for moderate facial acne and multiple violaceous striae on the abdomen. Blood tests show an elevated glucose level of 150 mg/dL, normal electrolytes, and renal function. His thyroid function tests are normal. You suspect idiopathic Cushing disease and order a dexamethasone suppression test to assist with confirming the diagnosis.

- Which pituitary hormone stimulates the release of adrenocortical steroids?
- What is the major glucocorticoid produced in the adrenal glands?
- What is the major mineralocorticoid produced in the adrenal glands?
- What is the major effect of mineralocorticoids?

ANSWERS TO CASE 41:
Adrenal Cortex

Summary: A 45-year-old man has Cushing disease.

- **Pituitary hormonal stimulus of adrenocortical steroid production:** ACTH.
- **Primary adrenal glucocorticoid:** Cortisol.
- **Primary adrenal mineralocorticoid:** Aldosterone.
- **Major mineralocorticoid effects:** Regulation of salt and water balance in the kidney, promote sodium retention, and potassium loss.

CLINICAL CORRELATION

Cushing disease is caused by ACTH-secreting tumors in the pituitary gland. The continuous production of ACTH disrupts the normal circadian production of ACTH and overrides the feedback of adrenal steroids on the hypothalamus and pituitary, resulting in excessive adrenocortical steroid production. Glucocorticoids affect most organs and tissues in the body. Their effects are mediated by specific intracellular glucocorticoid receptors that modulate the transcription rates of specific genes and results in increases or decreases of specific proteins. The major glucocorticoid produced in the adrenal glands is cortisol (hydrocortisone). Glucocorticoids have numerous physiologic effects, including the stimulation of gluconeogenesis, increasing lipolysis, decreasing glucose uptake into fat cells, and redistributing body fat. These effects cause some of the symptoms and signs of Cushing disease, which include glucose intolerance or overt diabetes, weight gain, and increasing truncal obesity. Glucocorticoids also have anti-immune effects, which include decreasing circulating lymphocytes, monocytes, eosinophils, and basophils, increases in circulating neutrophils and atrophy of lymphoid tissue. The excess production of glucocorticoids can therefore lead to immune system suppression and recurrent infections. Under normal physiologic conditions, adrenocortical steroids will exert a negative feedback of ACTH release from the pituitary gland. ACTH release, and subsequent cortisol production, can be suppressed even more by the administration of synthetic steroids such as dexamethasone. ACTH, which is continuously produced by a tumor, will not be suppressed by this feedback mechanism. This formulates the basis for the dexamethasone suppression test, in which a dose of dexamethasone is administered and subsequent cortisol production is measured. Normally dexamethasone administration would cause a reduction of circulating cortisol. In Cushing disease the measurement of cortisol will remain at normal, or even elevated, levels.

APPROACH TO:

Pharmacology of the Glucocorticoids

OBJECTIVES

1. Understand the physiologic regulation of the hypothalamic-pituitary-adrenal axis.
2. List the natural and synthetic adrenocortical steroids, their actions, therapeutic uses, and adverse effects.
3. Know the effects of glucocorticoids and mineralocorticoids.
4. Understand the adrenocortical antagonists, their mechanism of action, uses, and adverse effects.

DEFINITIONS

Glucocorticoids: In humans the most important glucocorticoid is cortisol. These hormones regulate carbohydrate, protein, and lipid metabolism.

Mineralocorticoids: In humans, aldosterone is the most important mineralocorticoid.

Aldosterone: It regulates Na^+ and K^+ homeostasis.

DISCUSSION

Class

Control of the secretion of glucocorticoids by the adrenal gland is regulated by a classic negative feedback pathway that includes the hypothalamus, pituitary, and the adrenal cortex (see Case 39). The **neuropeptide CRH is a 41-amino acid peptide produced in the hypothalamus** that is **secreted with a circadian rhythm.** Secretion can also be increased by physiologic or psychologic stress. **CRH acts on the pituitary to stimulate the release of ACTH**. ACTH released from the pituitary is transported in the systemic circulation to the **adrenal cortex,** where it acts to stimulate the **zona fasciculata and reticularis to increase the biosynthesis of cortisol and weak androgens** such as **androstenedione,** respectively. It also acts on the **zona glomerulosa** to slightly stimulate the production of **aldosterone.** ACTH is a true trophic hormone: it is necessary for the survival of cells of the adrenal cortex, although this effect is somewhat less pronounced in the zona glomerulosa. Cortisol secreted by the adrenal cortex is bound extensively to cortisol-binding globulin (CBG) in the plasma.

Glucocorticoids **Natural and synthetic glucocorticoids** play a diverse role in **metabolism, catabolism, and immunity.** Both cortisol, the natural glucocorticoid, and many synthetic glucocorticoids are used therapeutically (Table 41–1). The synthetic glucocorticoids have reduced mineralocorticoid activity and in general increased potency compared to cortisol. Glucocorticoids have a myriad of

Table 41–1 • COMMONLY USED ADRENOCORTICAL AGENTS				
	Equivalent Dose	Glucocorticoid	Mineralocorticoid	Anti-Inflammatory
Agent (mg)		Potency	Potency	Potency
Cortisol	20	100	1	1
Prednisone	5	100	0.4	4
Methylprednisolone	4	100	0.1	4
Triamcinolone	4	100	0.1	5
Dexamethasone	0.75	100	0.05	30
Fludrocortisone	2	100	250	10

therapeutic uses. They are potent **anti-inflammatory agents** because they **stimulate annexin A1.** Annexin A1 has a number of anti-inflammatory actions including inhibition of cytokine production**,** inhibition of prostaglandin production, and inhibition of immune cells. Unlike nonsteroidal anti-inflammatory drugs (NSAIDs), they **inhibit leukocytes and macrophages that contribute heavily to inflammation.** Glucocorticoids are used to treat joint and bone inflammation, inflammatory bowel disease, bronchial asthma (first-line therapy), and dermatitis. Systemic inflammations such as in lupus erythematosus, rheumatoid arthritis, and acute respiratory distress syndrome are also treated with glucocorticoids. Glucocorticoids are potent immunosuppressive agents and are used either alone or in conjunction with other immunosuppressive agents to suppress organ rejection following transplant, and to reduce the severity of allergic reactions including contact dermatitis, serum sickness, and allergic rhinitis. Other uses include prevention of respiratory distress syndrome in infants (by induction of surfactant), prevention of nephrotic syndrome, and at high doses to reduce cerebral edema. Adrenal insufficiency either acute or congenital is treated with glucocorticoids. Finally glucocorticoids are useful diagnostically as in the dexamethasone suppression test described above.

Although they are highly efficacious agents, the **adverse effect profile** of glucocorticoids limits their use typically to short (approximately 2 weeks) periods. **Chronic use of glucocorticoids** beyond this duration produces **adrenal suppression** and can cause iatrogenic Cushing syndrome. The metabolic sequelae of **Cushing syndrome** include **fat redistribution (buffalo hump and moon facies), hyperglycemia,** and **elevations in insulin secretion leading to frank diabetes.** Continued protein degradation can cause **myopathy** and **muscle wasting,** and **thinning of the skin** that becomes prone to **bruising and striae. Immunosuppression** leads to susceptibility to infection and poor wound healing. **Peptic ulcers and osteoporosis** are other potential consequences of glucocorticoid use. **Adrenal suppression** occurs with chronic glucocorticoid use as a result of continuous suppression of ACTH production by the pituitary. The absence of the trophic hormone leads to adrenal atrophy and an inability to respond to stress, which can be life-threatening. Neurological adverse effects include **hypomania, acute psychosis, and depression.** At sufficient doses, all glucocorticoids have some mineralocorticoid activity that can lead to **electrolyte imbalances and water retention.**

Mineralocorticoids **Aldosterone** is the naturally occurring mineralocorticoid. It is secreted by the **zona glomerulosa of the adrenal cortex. Secretion of aldosterone is increased by angiotensin II and K^+, especially when serum Na^+ is low.** The physiologic action of aldosterone is to **increase Na^+ reabsorption** in the distal convoluted tubule and cortical collecting tubule via the amiloride-sensitive Na^+ channel. As Na^+ is reabsorbed, K^+ or H^+ is secreted into the urine and water is retained. Aldosterone also causes Na^+ reabsorption in the salivary and sweat glands and the mucosa of the gastrointestinal (GI) tract. Aldosterone is not useful as an oral agent because of a nearly 100 percent first-pass effect by the liver. **Fludrocortisone** (see Table 41–1) has both glucocorticoid and mineralocorticoid activity. An alternative to fludrocortisone is **deoxycorticosterone (DOC),** which is a potent mineralocorticoid.

Structure

Synthetic glucocorticoids are all analogs of the natural occurring cortisol. Various modifications of the steroid nucleus have important pharmacokinetic effects to increase glucocorticoid potency relative to mineralocorticoid potency, to decrease first-pass effect and increase half-life, and to decrease binding to CBG. Aldosterone has a unique epoxide structure in the "D" ring that prevents its inactivation.

Mechanism of Action

Both the **glucocorticoids and the mineralocorticoids** bind to **specific nuclear receptors within target cells.** The **glucocorticoid receptor** is in an inactive state in the cytoplasm of target cells bound to a variety of heat-shock proteins, especially HSP 90. On binding a glucocorticoid, the heat-shock proteins dissociate, the GR forms a homodimer and **translocates to the nucleus** and binds to the **promoter region of specific target genes.** Via the process of coactivator or corepressor recruitment, transcription of specific target genes is either increased or decreased. The mineralocorticoid receptor (MR) is expressed in the kidney, salivary glands, and GI tract. It binds aldosterone with high affinity but also binds cortisol with nearly the same affinity. MR bound to cortisol is held in an inactive state by NADH produced by the enzyme 11β-HSD2.

Administration

Glucocorticoids can be administered orally, by injection, by inhalation (especially for use in asthma), rectally, and topically. Patients taking glucocorticoids for longer than 2 weeks must be slowly tapered off the drug so that adrenal function can be restored. When used for less than 10–14 days, systemic glucocorticoids cause insignificant adrenal suppression and tapering is not necessary.

Pharmacokinetics

The half-life and duration of action of glucocorticoids depend on the route of administration and the particular agent. In general, glucocorticoid effects are seen within 4–6 hours. Most corticosteroids are metabolized in the liver to sterol ketones or hydroxides and eliminated by the kidney.

Glucocorticoid and Mineralocorticoid Antagonists There are some clinical circumstances such as inoperable adrenal tumors, prior to surgery and for diagnostic use, where **inhibition of glucocorticoid action** is desirable. **Metyrapone** is a **specific inhibitor of 11-hydroxylation,** and can thereby inhibit **the synthesis of corticosterone and cortisol.** In the presence of normal pituitary function there is a **compensatory increase in 11-deoxycortisol production. Metyrapone is also useful in the assessment of adrenal function.** Following metyrapone administration, urinary 17-hydroxysteroids, metabolites of adrenal glucocorticoid synthesis, typically double if the adrenals are functioning normally. **Chronic metyrapone can cause hirsutism, nausea, sedation, and rash.**

Aminoglutheamide blocks the conversion of cholesterol to pregnenolone. This **inhibits the synthesis of all hormonally active steroids.** It has been used to reduce glucocorticoid levels in patients with Cushing syndrome because of adrenal tumors or excessive ectopic production of ACTH. It has also been used to treat

estrogen-dependent breast cancer and prostate cancer. Adverse effects are common and include GI upset and neurologic disturbances.

Ketoconazole is an **antifungal agent;** at high doses it **nonspecifically blocks several enzymes, especially P450 enzymes** that are involved in adrenal and gonadal steroidogenesis. It is the most effective inhibitor of steroid hormone biosynthesis available in patients with Cushing disease. **Adverse effects include hepatic dysfunction with increased transaminases and liver failure.**

Mifepristone (RU-486) is a 19-nor steroid that is a potent antagonist of both the glucocorticoid and progesterone receptors. It has been used to reduce the activity of glucocorticoids in patients with ectopic ACTH production or adrenal carcinoma. The main use of mifepristone is as an antiprogestin (Case 40) as an abortifacient when combined with prostaglandin E_1.

Two mineralocorticoid antagonists are available, spironolactone and eplerenone. Spironolactone antagonizes the mineralocorticoid and the androgen receptor (AR). It is used to treat hypertension (see Case 12) usually in combination with a thiazide or a loop diuretic. It can be used diagnostically to restore potassium levels to normal in patients with hypokalemia secondary to hyperaldosteronism. Based on its **antiandrogen activity,** it has been **used to treat hirsutism in women.** Adverse effects include **hyperkalemia, sedation, cardiac arrhythmias, gynecomastia, sedation, headache, and GI upset.**

Eplerenone is a **new-generation, aldosterone receptor–specific antagonist.** It is approved for use in **congestive heart failure, post-myocardial infarction, and hypertension.** It **avoids the antiandrogen activity of spironolactone. Adverse effects** include mild **hyperkalemia,** dizziness, cough, and fatigue.

COMPREHENSION QUESTIONS

41.1 Which of the following best describes appropriate protocols for withdrawal of glucocorticoids from a patient who has been taking large doses for 6 months?

A. Maintain dose of glucocorticoids and add metyrapone.

B. Maintain dose of glucocorticoids and add spironolactone.

C. An alternate-day dosage regimen of glucocorticoids should be begun.

D. Slow reduction of the glucocorticoid dose over 1–2 weeks.

41.2 A patient with severe shoulder pain resulting from inflammation is not responding to treatment with naproxen. You elect to begin a course of treatment with oral dexamethasone. What is the basis that the glucocorticoid will be more effective as an anti-inflammatory agent?

A. Glucocorticoids inhibit both prostaglandin production and inflammatory cells.

B. Glucocorticoids are more potent inhibitors of cyclooxygenase than naproxen.

C. Glucocorticoids inhibit biosynthesis of both COX-1 and COX-2.

D. Glucocorticoids will reduce the edema in the inflamed area.

41.3 A 32-year-old woman is prescribed a pill for excessive hair on her face and arms. She notes that she has been going to the bathroom at night more often. What is the most likely explanation for the nocturia?

A. Diabetes insipidus effect of the medication

B. Osmotic load to the kidney from the medication delivery system

C. Distal renal tubule effect of the medication

D. Hyperglycemic effect from the medication

ANSWERS

41.1 **D.** Long-term use of glucocorticoids results in adrenal suppression and atrophy. A slow "weaning" from the drug is necessary so that the adrenals can recover.

41.2 **A.** Glucocorticoids reduce prostaglandin production like NSAIDs and they also inhibit most of the cells that are involved in the inflammatory process.

41.3 **C.** The medication is probably spironolactone, which is a competitive inhibitor of androgens at the receptor level, and also an antimineralocorticoid effect at the distal tubule, inhibiting free water resorption. As such, it is a potassium-sparing diuretic agent.

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CASE 42

A 44-year-old woman presents to the office because of fatigue. She has felt sluggish for months and thinks she may be anemic. She has started taking iron pills but isn't feeling any better. She has been sleeping well and doesn't feel depressed. She has noticed some thinning of her hair and feels as if her skin is dry. She takes a multivitamin and iron supplement, otherwise no medications. She has smoked a pack of cigarettes a day for approximately 20 years, occasionally drinks alcohol, and doesn't exercise. Her mother takes some kind of thyroid pill and has diabetes. On examination, her blood pressure and pulse are normal. Her hair is thinned but there are no focal patches of alopecia or scarring of the scalp. Her skin is diffusely dry. Her thyroid gland feels diffusely enlarged, is nontender, and has no nodules. The remainder of her examination is unremarkable. Lab tests show a normal complete blood count (CBC), glucose, and electrolytes. Her thyroid-stimulating hormone (TSH) level is elevated, and T_4 level is reduced. You diagnose her with hypothyroidism and start her on oral levothyroxine sodium.

- What is levothyroxine sodium?
- How is triiodothyronine (T_3) produced in the body?
- What is the mechanism of action of thyroid hormones?

ANSWERS TO CASE 42:
Thyroid Hormones

Summary: A 44-year-old woman is diagnosed with hypothyroidism and prescribed levothyroxine.

- **Levothyroxine sodium:** Synthetic sodium salt of thyroxine (T_4).
- **Derivation of T_3 in the body:** Approximately 75 percent from the deiodination of T_4; also produced by the coupling of monoiodotyrosine (MIT) and diiodotyrosine (DIT).
- **Mechanism of action of thyroid hormones:** Bind with receptors in nuclei of target cells and alter synthesis rates of specific messenger ribonucleoprotein acids (mRNAs), increasing production of certain proteins including Na^+, K^+-ATPase.

CLINICAL CORRELATION

Thyroid hormones have wide-ranging effects of tissues throughout the body. They are involved primarily in the regulation of metabolism. The hypothalamic-pituitary-thyroid axis regulates release of active hormone from the thyroid via a feedback loop. Thyrotropin-releasing hormone (TRH) is produced in the hypothalamus and stimulates the release of TSH from the anterior pituitary. TSH binds to membrane receptors in the thyroid and stimulates the production and release of T_4 and T_3 via a cyclic adenosine monophosphate (cAMP)-mediated system. Synthesis of T_4 exceeds T_3 by approximately fourfold; most circulating T_3 comes from peripheral deiodination of T_4. T_4 and T_3 are almost entirely protein bound, mostly to thyroxine-binding globulin (TBG) and albumin. Unbound thyroid hormone binds to receptors located in the nuclei of target cells. This alters transcription of specific mRNAs, which lead to the increased production of proteins, including Na^+, K^+-ATPase. This results in a net increase in ATP and oxygen consumption, raising the metabolic rate. Hypothyroidism occurs when there is inadequate thyroid hormone production and release to meet the body's metabolic demands. In primary hypothyroidism the thyroid gland is unable to synthesize adequate amounts of thyroid hormone. The pituitary releases increasing amounts of TSH to try to stimulate production, leading to the characteristic laboratory findings of low circulating levels of thyroid hormones with an elevated TSH. Conversely, primary hyperthyroidism is diagnosed by the presence of elevated thyroid hormone levels and a suppressed level of TSH. Hypothyroidism is most often treated by the oral administration of synthetic T_4 in the form of levothyroxine sodium. This replaces both T_4 and, by deiodination, T_3.

APPROACH TO:

Pharmacology of Thyroid Drugs

OBJECTIVES

1. List the hormones involved in the hypothalamic-pituitary-thyroid axis and the synthesis of thyroid hormones.
2. Know the actions of thyroid hormones.
3. List the thyroid hormone preparations, their therapeutic uses, actions, and adverse effects.
4. Describe the antithyroid agents, their mechanisms of action, therapeutic uses, and adverse effects.

DEFINITIONS

Myxedema: The nonpitting edema of the skin and soft tissue that occurs in patients who are hypothyroid. Myxedema coma is an extreme complication of hypothyroidism in which patients exhibit multiple organ abnormalities and progressive mental deterioration. The cardinal manifestation of myxedema coma is a deterioration of the patient's mental status even without coma.

Thyrotoxicosis: Hyperthyroidism.

DISCUSSION

Class

Thyroid Agonists **Thyroid hormones are required for optimum development, growth, and maintenance of function of virtually every tissue of the body.** Either hypo- or hyperthyroidism leads to untoward symptoms that need to be treated. The thyroid gland produces both thyroxine (T_4) and triiodothyronine **(T_3).** Adequate dietary intake of sufficient **iodide (I^-) is essential** to maintain normal biosynthesis of thyroid hormones. **Iodide is transported into the thyroid cell by a sodium-iodide symporter (NIS)** and then transported through the **apical plasma membrane into the colloid of the thyroid** gland. Within the colloid, **iodide is oxidized to iodine by thyroidal peroxidase.** The process called organification involves the iodination of tyrosine residues of the colloidal protein thyroglobulin to form **MIT and DIT.** The coupling of two molecules of DIT forms T_4 and the coupling of one molecule of MIT, and one molecule of DIT forms T_3. Under normal circumstances and sufficient iodide, the ratio of T_4 to T_3 is 4:1. T_3 can also be formed by the removal of an iodide molecule from T4 by the action of 5'-deiodinase, which is present within the thyroid gland and in peripheral tissues.

Iodinated thyroglobulin undergoes endocytosis at the apical border and then is extensively degraded within the thyroid cells by proteolysis prior to secretion of T_4 and T_3. Although T_3 is produced with the thyroid, approximately **80 percent**

of circulating levels of T_3 are produced by the action of 5'-deiodinase in the periphery, especially the **liver.** Alternatively T_4 can be *degraded* by the action of deiodinase to reverse T_3, which is an inactive metabolite. Normally approximately 40 percent of T_4 is converted to T_3, 38 percent is converted to rT_3, and the remainder is degraded by other, typically hepatic pathways. Greater than 99 percent of both T_4 and T_3 are bound in the plasma to TBG; T_4 binds to TBG much more avidly. **Only the unbound "free" hormone exerts physiologic effects.**

Secretion of thyroid hormones is regulated by a **classical hypothalamus-pituitary-thyroid negative feedback loop. TRH is produced within hypothalamus.** It acts on **thyrotrophs in the pituitary to cause the release of thyrotropin (TSH),** which in turn stimulates all steps in the **biosynthesis and secretion of thyroid hormones.** Circulating levels of thyroid hormone decrease the amount of TRH that is released from the hypothalamus, completing the feedback loop. Somatostatin and dopamine reduce TSH release.

Thyroid hormone is critical for normal brain development. The **absence of normal thyroid hormone function in the first months of the infant leads to irreversible cretinism.** Thyroid hormone induces myelin basic protein, and hypothyroidism leads to decreased production of this protein and defective neuronal myelination. Thyroid hormones have an important effect on oxygen consumption in many tissues including heart, skeletal muscle, kidney, and liver; brain, gonads, and spleen are not affected. This calorigenic effect is important to normal thermogenesis. Thyroid hormones also increase lipolysis.

Thyroid hormone has direct actions on the heart and vascular system. Hyperthyroidism leads to tachycardia, increased stroke volume, increased pulse pressure, and decreased vascular resistance. Hypothyroidism leads to bradycardia, and the opposite of the above effects. Thyroid hormones increase the conversion of cholesterol to bile and increase LDL uptake by the liver and thereby reduce plasma cholesterol concentrations.

Hypothyroidism can be treated effectively by hormone replacement. Common causes of hypothyroidism include **autoimmune destruction** of the thyroid gland **(Hashimoto disease), congenital hypothyroidism, or impaired pituitary or hypothalamic function.** Thyroid hormones are indicated for the treatment and prophylaxis of goiter by suppressing abnormal growth of the thyroid gland. Thyroid hormones are also useful in the treatment of TSH-dependent thyroid cancers. Adverse effects of thyroid hormones are a hyperthyroid state with increased calorigenesis and oxygen demand, tachycardia, and increased cardiac workload.

Structure

Synthetic preparations of T_4 (levothyroxine), T_3 (liothyronine) and a 4:1 mixture of T_4/T_3 (liotrix) are preferable to desiccated preparations of thyroid prepared from animals that are more variable in biologic activity.

Mechanism of Action

The actions of the thyroid hormones are mediated by nuclear thyroid receptors that act by increasing or decreasing transcription of target genes. There are three major

thyroid receptors: $TR\beta_1$, $TR\beta_2$, and $TR\alpha_1$. Whereas $TR\beta_1$ and $TR\alpha_1$ are expressed in virtually every tissue, $TR\beta_2$ is expressed exclusively in the anterior pituitary. These receptors bind T_3 in the nucleus. T_4 can bind to the receptors but at much lower affinity and with much less, if any, effect on transcription. Thyroid receptors are bound in the absence of ligand to the promoters of target genes, and in some cases the nonliganded receptor exerts a potent inhibition of basal transcription. T_3 binding to TR results in recruitment of coactivators and subsequent disinhibition and increased rates of transcription. All the above preparations of thyroid hormone can be administered orally. Levothyroxine and liothyronine are also available for parenteral administration. Doses are individualized and monitored by measuring the level of circulating TSH.

Pharmacokinetics

T_4 has a very long half-life (7 days), in large part because of its extensive binding to TBG. The half-life of T_4 is lengthened to 9–10 days in hypothyroidism and decreased to 3–4 days in hyperthyroidism. Thyroid hormones are degraded mostly by the liver and excreted in the bile.

Thyroid Antagonists **Hyperthyroidism** can be treated with agents that **decrease the biosynthesis of thyroid hormones,** or **destroy** of the **thyroid gland with radioactive isotopes** of thyroid hormones or surgery. The **thioamides, methimazole and propylthiouracil (PTU),** are the major drugs for treating hyperthyroidism. These drugs act by **inhibiting peroxidation of iodide and organification of thyroglobulin. PTU** also acts to **inhibit the coupling reaction that forms MIT and DIT.** PTU is preferred over methimazole in women of child bearing age. Although complications in pregnancy are rare for both agents, PTU has had better safety profile for longer term than methimazole. Methimazole offers the advantage of less frequent dosing.

Adverse effects of **thioamides** include a **maculopapular rash, and less commonly arthralgia, skin rashes, hepatoxicity, cholestatic jaundice, and a lupus-like syndrome.** Potentially life-threatening **agranulocytosis** has occurred with their use.

Historically, iodides were the major antithyroid agents. Large oral doses of iodide inhibit organification and the secretion of thyroid hormones. **Iodide is useful in treating acute thyrotoxicosis (thyroid storm),** and to reduce the size, vascularity, and fragility of a hyperplastic thyroid preoperatively. Most patients will escape the blocking effects of iodide in 2 to 8 weeks.

Monovalent anions such as perchlorate (ClO_4^-), thiocyanate (SCN^-), and pertechnetate (TCO_4^-) are competitive inhibitors of the iodide transport mechanism, but rarely used compared to thioamides due to adverse effects.

Radioactive iodine-131 is rapidly trapped and concentrated in the colloid of the thyroid gland exactly as occurs with the stable ^{127}I. Radiation is nearly exclusively delivered to the parenchymal cells of the thyroid and leads to a dose-dependent destruction of part or the entire gland. In many circumstances it is considered the treatment of choice for chronic hyperthyroidism. It should not be used in patients who are pregnant because of its action on the thyroid of the fetus.

COMPREHENSION QUESTIONS

42.1 A woman enters your clinic with an enlarged thyroid and you suspect simple adenomatous goiter. The serum TSH is elevated. Which of the following would be the best treatment for this condition?

A. IV infusion of TSH
B. Levothyroxine
C. Propylthiouracil
D. Thyroid ablation with ^{131}I

42.2 The mechanism by which thiocyanate reduces synthesis of thyroid hormones is by inhibition of which of the following?

A. Iodine oxidation
B. Iodide transport
C. TSH biosynthesis
D. TRβ

42.3 A 33-year-old man is noted to have tachycardia, heat intolerance, weight loss, and an enlarged thyroid gland. Which of the following is the probable ultimate treatment for this patient?

A. Long-term corticosteroid therapy
B. Propranolol therapy
C. Radioactive iodine
D. Surgical resection

ANSWERS

42.1 **B.** Hypothyroidism is an indication for thyroid hormone replacement.

42.2 **B.** Anions such as perchlorate and thiocyanate inhibit the transport of iodide into thyroid cells.

42.3 **C.** This patient likely has Graves disease, the most common cause of hyperthyroidism in the United States, typically presenting with a painless goiter and symptoms of hyperthyroidism. The treatment of choice is radioactive iodine. Propanalol will help with the symptoms of tachycardia but not the underlying disease process.

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CASE 43

A 12-year-old boy is brought to the office by his parents because of abdominal pain for the past day. Prior to this, the parents noted that he was drinking a lot of water and going to the bathroom frequently. He said that his mouth was very dry and he was very thirsty. Until the past day or two he was eating more than usual but was losing weight. He has no significant medical history, and the family history is unremarkable. On examination, he appears moderately ill, and his blood pressure is normal, but he is tachycardic. His mucous membranes are dry. His abdomen is diffusely tender but without rebound or guarding. A urine dipstick test in the office reveals the presence of large ketones and glucose. A glucose measurement from a drop of blood obtained by finger stick is markedly elevated at 550 mg/dL. You immediately admit the patient to the hospital for newly diagnosed type I diabetes mellitus in ketoacidosis and start an infusion of IV fluids and regular insulin.

- What is the structure of natural human insulin?
- What effect does insulin have on potassium?
- What is the effect of α-adrenergic stimulation on insulin secretion?
- What is the effect of β-adrenergic stimulation on insulin secretion?

ANSWERS TO CASE 43:

Pancreas and Glucose Homeostasis

Summary: A 12-year-old with newly diagnosed type I diabetes mellitus has ketoacidosis.

- **Structure of human insulin:** A 51-amino acid polypeptide that consists of two chains linked by two disulfide bridges.
- **Effect of insulin on potassium:** Promotes cellular K^+uptake.
- **Effect of α-adrenergic stimulation:** Inhibition of insulin secretion.
- **Effect of β-adrenergic stimulation:** Increased insulin secretion.

CLINICAL CORRELATION

Insulin is a 51-amino acid polypeptide that is produced in pancreatic β cells and stored as a complex with Zn^{2+}. The primary stimulus for insulin release is glucose, but amino acids, fatty acids, and ketone bodies may stimulate its release. Glucagon and somatostatin also modulate its secretion. α-Adrenergic stimulation is a predominant inhibitory mechanism, whereas β-adrenergic stimulation increases its release. Insulin acts by binding to specific membrane receptors that have tyrosine kinase activity. Tyrosine in the receptor becomes phosphorylated and the phosphoreceptor in turn phosphorylates a number of intracellular substrates that lead to increased glucose uptake. In muscle and adipose tissue, glucose transport is mediated by the recruitment of hexose transport molecules (GLUT-4) into the plasma membrane. Among its many actions, insulin increases glucose transport, glycogen synthesis and deposition, lipogenesis, and protein synthesis. It decreases intracellular lipolysis and hepatic gluconeogenesis. Insulin also stimulates cellular potassium accumulation. Type I diabetes mellitus is a disease in which pancreatic β cells fail to produce adequate amounts of insulin. Insulin must then be supplemented. Currently used insulin preparations are all human insulin produced by recombinant deoxyribonucleic acid (DNA) techniques. There are short-, intermediate-, and long-acting insulin preparations available. The most widely used insulin products must be given by injection, usually requiring 1–4 subcutaneous injections a day or continuous subcutaneous infusion with an insulin pump. Regular insulin can also be given intravenously in the setting of diabetic ketoacidosis. An insulin product was available for inhalation use but it was removed from the market due to lack of demand, need for high doses, and need for recurrent lung function monitoring. Another inhaled insulin is going to be introduced shortly. Insulin injections are also used in type II diabetics, who cannot achieve adequate control with oral agents. The most significant risk of insulin therapy is the induction of hypoglycemia. Hypoglycemia may produce tachycardia, sweating, and confusion. In severe cases, hypoglycemia may progress to coma, seizures, or even death.

APPROACH TO:

Pharmacology of Insulin and Oral Hypoglycemic Agents

OBJECTIVES

1. List the structure and function of endogenous insulin.
2. Know the characteristics, therapeutic uses, and adverse effects of insulin preparations.
3. Understand the mechanisms of action, uses, and adverse effects of oral hypoglycemic agents.
4. Understand the mechanisms of action, uses, and adverse effects of agents used to raise blood sugar levels.

DEFINITIONS

Type I diabetes: Historically called juvenile onset diabetes or insulin-dependent diabetes mellitus (IDDM), it is a hyperglycemic condition caused by inadequate production of insulin by β cells of the pancreas.

Type II diabetes: A condition of hyperglycemia caused by resistance to circulating levels of insulin. Also called non-insulin-dependent diabetes mellitus (NIDDM). Although NIDDM starts off as insulin resistance, eventually patients may require insulin to control their blood sugar. Eventually, these patients can lose all of their pancreatic β-cell function and ability to produce insulin and hence become insulin dependent. The incidence of this condition is increasing markedly in the United States and is especially prevalent in the Hispanic community.

DISCUSSION

Class

Insulin is secreted by the B cells of the pancreas. The islet of Langerhans within the pancreas is made of four cell types; each secretes a distinct polypeptide. The **B (or β) cells secrete insulin, A (or α) cells secrete glucagon, D (or δ) cells secrete somatostatin,** and the PP or F cells secrete pancreatic polypeptide. **Human insulin comprises two chains, the A and B chains,** that are produced by the formation of **one intrapeptide and two interpeptide disulfide bonds** from a 110-amino acid precursor called **preproinsulin.** This precursor is cleaved within the endoplasmic reticulum and Golgi complex to form mature insulin and C-peptide. Insulin secretion is a tightly regulated process that normally maintains a stable concentration of plasma glucose through both postprandial periods and periods of fasting. **Glucose is the most important stimulus to insulin secretion in humans.** Insulin secretion is also stimulated by GI inhibitory polypeptide 1, glucagon-like peptide 1, gastrin, secretin, cholecystokinin, vasoactive intestinal polypeptide, gastrin-releasing peptide, and enteroglucagon. Neural input via catecholamines also regulate insulin secretion as

stated above. **Glucose enters the pancreas via a specific transporter, GLUT-2,** and is **rapidly phosphorylated by glucokinase.** Glucokinase is considered to be the glucose sensor within the B cell and its activity ultimately leads to increased intracellular Ca^{2+} within the B cell and this causes insulin secretion. Insulin promotes the uptake of carbohydrates, proteins, and fats in most tissues. It influences metabolism by stimulating protein and free fatty acid biosynthesis and inhibits the release of fatty acids from adipose cells. Insulin stimulates the production of glycogen and triglycerides. **Insulin is the mainstay for the treatment of virtually all type I diabetics** and many type II diabetics. There are several principal types available that differ in their onset and duration of action (Table 43–1).

The **goal of insulin therapy is to control plasma glucose levels as tightly as possible.** Most of the sequelae of diabetes such as **retinopathy, renal damage, and neuropathy** are caused by the **hyperglycemic condition** rather than the absence of insulin. Current regimens generally use an intermediate or long-acting preparation supplemented with injections of short- or rapid-acting preparations to meet postprandial needs. Premixed mixtures of different types of insulins are also available. An insulin powder for inhalation is in clinical trials for use in patients with type I and type II diabetes mellitus. Inhaled insulin uses a device similar to an asthma inhaler for fixed insulin dosage prior to meals. The most common adverse effect of insulin administration is **hypoglycemia.**

Structure

Human insulin derived by recombinant technology in bacteria or yeast has supplanted the use of bovine or pork insulins.

Mechanism of Action

All of insulin's activities are mediated by the insulin receptor, which is expressed in most tissue types. The insulin receptor consists of an extracellular α-subunit that forms the insulin-binding site and a transmembrane β-subunit that possesses tyrosine kinase activity. The mature insulin receptor is a dimer composed of two α-subunits

Table 43–1 • INSULIN PREPARATIONS

Agent	Time to Onset	Time to Peak Plasma Concentration (SQ)	Duration of Action (Hours)
Rapid acting (lispro, aspart, glulisine)	5-15 minutes	60-90 minutes	2-3
Short acting (regular insulin)	30 minutes	2-4 hours	5-8
NPH insulin	1-2 hours	4-9 h	8-16
Long acting insulin detemir	1-3 hours	6-8	6-24 (dose dependent)
Long acting insulin glargine	1-3 hours	No pronounced peak	24+

and two β-subunits. Insulin binds its receptor in the picomolar range within a binding pocket formed by the two α-subunits. Binding produces conformational changes in the receptor that activate intrinsic tyrosine kinase activity that results in autophosphorylation of one β-subunit by the other. This autophosphorylation increases the tyrosine kinase activity of the receptor toward other substrates, especially the docking proteins insulin-receptor substrate 1 (IRS-1) and IRS-2. Phosphorylation of IRS-1 and IRS-2 results in further downstream phosphorylation and activation of MAP kinase and phosphatidylinositol-3-kinase. This network of phosphorylation ultimately leads to translocation of glucose transporters, especially GLUT-4, to the plasma membrane. This results in an increase in glucose transport into muscle and adipose tissue. Phosphorylation of various substrates in this insulin pathway also increases glycogen synthesis, lipogenesis, protein synthesis, and activation of transcription factors that mediate effects on cell growth and division.

Administration

Most currently available preparations are injected subcutaneously or delivered by continuous infusion. Insulin glargine **cannot** be mixed with other insulins because of precipitation. Short-acting soluble insulin is the only form that should be administered IV.

Oral Hypoglycemic Agents

Oral hypoglycemic agents increase the secretion of insulin by the pancreas or alter tissue sensitivity to insulin. These agents are typically used to control hyperglycemia in patients with type II diabetes (Table 43–2).

Sulfonylureas

Sulfonylureas act to **increase the release of insulin from the pancreas. First-generation sulfonylureas** include tolbutamide, chlorpropamide, tolazamide, and acetohexamide. **Second-generation agents** include glyburide, glipizide, gliclazide, and glimepiride, which are considerably **more potent** than the earlier agents. All are **substituted arylsulfonylureas** with different substitutions on the benzene ring and at one nitrogen residue of the urea moiety. Sulfonylureas are used to control glucose levels in type II diabetics who cannot achieve adequate control with diet alone. A limitation in the use of the sulfonylureas is secondary failure, that is, failure to maintain glucose levels with chronic use. **Adverse effects of sulfonylureas include hypoglycemia, nausea and vomiting, anemia, and dermatologic reactions.**

Mechanism of Action **Sulfonylureas bind to a high-affinity sulfonylurea receptor on B cells that inhibits a K^+-efflux channel.** This leads to **depolarization of the cell with an increase in Ca^{2+} entry** through voltage-gated Ca^{2+} channels. The increased intracellular Ca^{2+} causes an increase in insulin secretion. Sulfonylureas **also stimulate the release of pancreatic somatostatin,** which can reduce the secretion of glucagon.

Administration All of the sulfonylureas are administered orally.

Pharmacokinetics First-generation sulfonylureas have relatively long half-lives: Chlorpropamide is 32 hours, tolazamide is 7 hours, and tolbutamide is 5 hours.

Table 43–2 • COMMON AGENTS FOR DIABETES

Medication	Mechanism of Action/Indications	Special Considerations	Reduction in HbA1c
Insulin	Supplement patient's own insulin production	Must check blood glucose frequently to monitor therapy and prevent complications	Unlimited
Sulfonylurea	Augments patient's own insulin production, works at the pancreatic B cells	Can cause hypoglycemia, can accumulate in renal insufficiency and cause prolonged hypoglycemia. Best for young patients with FPG <300mg/dL	1.5%
Biguanide Metformin	Increases glucose uptake by muscle, decreases gluconeogenesis in the liver, decreases insulin resistance	In patients with renal insufficiency, or liver dysfunction, may cause lactic acidosis	1.5%
α-Glucosidase inhibitors: Acarbose, Miglitol	Inhibits breakdown of complex carbohydrates in the GI tract	Can cause GI distress, and must be taken TID with meals. Dose-dependent hepatotoxicity	0.5-0.7%
Thiazoladinediones Pioglitazone	Promote skeletal muscle glucose uptake, decrease insulin resistance	Hepatoxicity, edema Contraindicated in Class III/IV heart failure. Can cause significant weight gain.	1-1.5%
Incretins: Exenatide	Increase insulin release and decrease glucagon production	Can cause hypersensitivity reactions. Nausea, weight loss	0.5-1%
DPP-4 inhibitor: Sitaglipin, Saxagliptin. Lingaglipin	Decreases breakdown of incretins	Cold-like symptoms, runny nose, sore throat. May be due to inhibition of cytokine breakdown	0.5-0.7%
Meglitinides: Repaglinide, Nateglinide	Nonsulfonylureas—but works in a similar manner—rapid onset of action. Monotherapy or in combination with metformin	Caution in elderly, renal, or hepatic insufficiency. Must dose TID with meals	0.5-1%

The second-generation agents tend to have shorter half-lives (approximately 4 hours), which makes them less prone to causing hypoglycemia. Sulfonylureas increase the rate at which beta cell failure will occur.

Other Insulin Secretagogues

Two relatively new insulin secretagogues, repaglinide and nateglinide, are approved for use in **type II diabetics.** Both of these agents act by **decreasing the activity of K^+ channels as described for the sulfonylureas.** This increases insulin release. Chemically, **repaglinide** is a **meglitinide,** and **nateglinide** is a **D-phenylalanine derivative.** Both have a half-life of approximately 1–1.5 hours and a very rapid onset of action that makes them well suited to **control postprandial increases in plasma glucose**. They should be taken approximately 10 minutes before a meal. Metabolized in the kidney and should be used cautiously in patients with renal impairment. Both these

drugs can cause hypoglycemia, but nateglinide has the lowest incidence of this adverse effect.

Insulin Sensitizers

Thiazolidinediones A **hallmark of type II diabetes is insulin resistance.** The hormone is present at significant plasma concentrations but is ineffective in reducing plasma glucose. **Thiazolidinediones (TZDs) act to increase tissue sensitivity to insulin.** TZDs appear to **increase glucose uptake in adipose and muscle tissues.** Two TZDs are approved for use: **pioglitazone and rosiglitazone.** The effects of the TZDs are mediated by agonist activity at the peroxisomal proliferator-activated receptor γ(PPAR-γ). PPARs are members of the nuclear receptor family that are present in the nucleus of cells tethered to the promoters of target genes. PPARs bind a rather diverse group of ligands, including fibrates and TZDs. There are three members of PPAR receptors: PPARα, PPARβ, and PPARγ; the last member mediates the effects of the TZDs. TZDs are effective in approximately 70 percent of type II diabetics. TZDs alter plasma lipid levels by reducing triglycerides, high-density lipoprotein (HDL), and low-density lipoprotein (LDL) cholesterol. TZDs should be avoided in CHF Stage III or higher.

Biguanides **Metformin lowers plasma glucose levels in the absence of functioning β cells;** it does not increase insulin secretion but **decreases insulin resistance** by increasing glucose uptake and decreasing glucose production. These actions are mediated by increasing the activity of AMP kinase. It is useful in patients with type II diabetes and **does not cause weight gain** or provoke hypoglycemia as do the sulfonylureas. Biguanides are frequently used in combination with TZDs or insulin secretagogues when monotherapy has not provided adequate glycemic control.

Common adverse effects include diarrhea, vomiting, nausea, and abdominal pain. Biguanides are **cleared by the kidney** and are **contraindicated in patients with renal disease.** The use of metformin is contraindicated in men with serum creatinine >1.5 and in women with serum creatinine >1.4.

Polypeptide Analogs **Pramlintide** is a synthetic analog of amylin, which is produced by the pancreas in concert with insulin. It decreases postprandial hyperglycemia and improves glucose control when administered with insulin. It is injected subcutaneously and is approved for treatment of both type I and type II diabetes.

Exenatide is a synthetic analog of glucagon-like polypeptide 1 (GLP-1), originally isolated from the saliva of the Gila monster, and is classified as an "incretin mimetic." The incretins include GLP-1 and glucose-dependant insulinotropic polypeptide (GIP) and are potent stimulators of insulin release and inhibitors of glucagon release. Exenatide mimics the enhancement of glucose-dependent insulin secretion and other antihyperglycemic actions of incretins. Several clinical trials have demonstrated the effectiveness of exenatide either with metformin or in combination with metformin and a sulfonylurea. Exenatide has been associated with weight loss and early satiety partly due to its side effect of nausea.

DPP-4 Inhibitors Endogenous enhancers of insulin release such as GLP-1 and GIP are inactivated by dipeptidyl peptidase 4 (DPP-4). The DPP-4 inhibitors block this

inactivation and thereby increase insulin secretion. Adverse effects include headache, nausea, hypersensitivity, and skin reactions. DPP-4 metabolizes some chemokines and inhibition of this peptidase may act to increase inflammatory cells and may be the cause of runny nose and sore throat seen with these drugs. The half-life of these drugs is 8–18 hours and they are administered orally once daily.

Other Enzyme Inhibitors **Monosaccharides** such as **glucose and fructose** can be absorbed across the intestine and into the portal circulation. Complex disaccharides, starches, and disaccharides that comprise a significant percentage of the carbohydrates ingested must be broken into monosaccharides before they can be absorbed. Pancreatic α-amylase and α-glucosidases are primarily responsible for this hydrolysis of more complex carbohydrates. **Inhibitors of α-glucosidase such as acarbose and miglitol inhibit the intestinal breakdown of complex carbohydrates. Acarbose** inhibits the α-glucosidases, sucrase, maltase, glucoamylase, dextranase. It weakly inhibits α-amylase. **Miglitol** is five to six times more potent than acarbose and inhibits the same α-glucosidase, as well as isomaltase and β-glucosidases (responsible for hydrolysis of lactose). Inhibition of these digestive enzymes reduces postprandial absorption of complex carbohydrates and thereby reduces plasma glucose levels. They are approved for treatment of type II diabetes as monotherapy or combined with a sulfonylurea if additional hypoglycemic effect is needed. **Adverse effects include flatulence, diarrhea, and abdominal pain,** most likely caused by the increase in carbohydrates in the distal small intestine and colon. α-Glucosidase inhibitors prevent the progression from a prediabetic state into new cases of type II diabetes and this may become a new indication for these drugs.

Agents That Increase Plasma Glucose **Glucagon** is useful for the **emergency treatment of severe hypoglycemia** when **unconsciousness prevents oral administration of nutrients and IV glucose is unavailable.** Glucagon binds to specific receptors in the **liver** that **increase cAMP** and promote the catabolism of glycogen into glucose. Glucagon must be administered parenterally.

COMPREHENSION QUESTIONS

43.1 Which of the following is the goal of insulin therapy?

A. Control serum glucose as tightly as possible
B. Control triglyceride biosynthesis
C. Maintain adequate hepatic glycogen stores
D. Maintain serum K^+ homeostasis

43.2 The thiazolidinediones are useful in treating type II diabetes because they have which of the following effects?

A. Decrease the degradation of insulin
B. Increase insulin release
C. Increase glucose utilization
D. Increase glucose uptake in muscle cells

43.3 A 42-year-old man is diagnosed with diabetes mellitus. He has tried diet and exercise without success. A second-generation sulfonylurea agent is prescribed. Which of the following is the most likely side effect he will experience?

A. Agranulocytosis
B. Hypoglycemia
C. Lactic acidosis
D. Myositis

43.4 A 45-year-old female with past history of type II diabetes mellitus presents for routine follow-up. Her fasting blood sugars are controlled in the 80–100 range. However, on your lab report the hemoglobin A1c is elevated at 8.5. You presume that she needs better mealtime glucose control. She is already on an oral biguanide and oral sulfonylurea. Which of the following agents would help with her prandial or mealtime glucose control without persisting in her system to cause later hypoglycemia?

A. Insulin detemir
B. NPH insulin
C. Repaglinide
D. Insulin aspart

ANSWERS

43.1 **A.** The goal in treating diabetes is tight control of serum glucose to avoid the complications of hyperglycemia.

43.2 **D.** The TZDs are insulin sensitizers; they do not alter insulin secretion or degradation but act to increase glucose uptake in adipose and muscle.

43.3 **B.** In general, the most common adverse effect of the agents for diabetes is hypoglycemia.

43.4 **D.** Insulin aspart is a rapidacting insulin ideal for mealtime glucose control as its onset is 5–15 minutes and duration is on average 2–3 hours. NPH and detemir insulin have longer durations of action and may combine with the oral sulfonylurea and insulin glargine to cause hypoglycemia later on. Repaglinide is a fair option, however, in general patients on sulfonylureas should not be on repaglinide or nateglinide as they have similar mechanisms of action.

PHARMACOLOGY PEARLS

- The goal in treating diabetes is tight glucose control to prevent the micro- and macrovascular complications.
- Human recombinant insulin is preferable to either bovine or porcine insulin.
- Biguanides such as metformin are cleared by the kidney and are contraindicated in patients with renal disease.
- Glucagon is useful for the emergency treatment of severe hypoglycemia when unconsciousness prevents oral administration of nutrients and IV glucose in unavailable.

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CASE 44

A 66-year-old woman presents for an annual health maintenance visit. She is generally feeling well and has no specific complaints. She takes hydrochlorothiazide for hypertension, levothyroxine sodium for hypothyroidism, and a multivitamin. She went through menopause at age 48 and never took hormone replacement therapy. She is a former cigarette smoker, having a 30 pack-year history and having quit 20 years ago. She occasionally has a glass of wine with dinner and walks three or four times a week for exercise. On examination you note that her height is 1 inch less than it was 3 years ago. Her vital signs are normal. She has a prominent kyphoscoliosis of the spine. Her examination is otherwise unremarkable. Blood work reveals normal electrolytes, renal function, blood count, calcium, and thyroid-stimulating hormone (TSH) levels. You order a bone density test, which shows a significant reduction of density in the spine and hips. You diagnose her with osteoporosis and start her on alendronate sodium.

- What is the mechanism of action of parathyroid hormone (PTH) on the bone and in the kidney?
- What is the mechanism of action of alendronate sodium?

ANSWERS TO CASE 44:
Agents Affecting Calcium Homeostasis

Summary: A 66-year-old woman with osteoporosis is prescribed alendronate.

- **Mechanism of action of PTH on the bone:** Pulsatile administration, the normal physiologic mode, enhances bone formation. Continuous delivery, for example, as a consequence of a parathyroid tumor, results in bone resorption.
- **Mechanism of action of PTH in the kidney:** Increases reabsorption of $Ca^{2+}$and $Mg^{2+}$and increases production of vitamin D and the active metabolite calcitriol and decreases reabsorption of phosphate, bicarbonate, amino acids, sulfate, sodium, and chloride.
- **Mechanism of action of alendronate sodium:** Inhibition of osteoclastic activity in bone, which reduces bone reabsorption.

CLINICAL CORRELATION

PTH has multiple actions on bone. Chronic elevations in PTH, for example, from a tumor, stimulate the resorption of bone via its stimulation of the number and activity of osteoclasts. This is mediated by specific PTH receptors in the bone, coupled to an increase in cyclic adenosine monophosphate (cAMP). Intermittent administration of PTH stimulates bone growth. Estrogen is an indirect inhibitor of PTH activity in the bone. This effect allows premenopausal women to maintain higher levels of bone density. Following menopause, with the resultant decrease in circulating estrogen levels, there is a relative increase in osteoclastic activity and resorption of bone, with a net loss of bone mineral density. Alendronate sodium is an analog of pyrophosphate that directly binds to bone. It inhibits osteoclastic activity, reducing the resorption of bone. This retards the progression of bone density loss and may allow for increases in density, because osteoblastic activity is not affected. It is administered orally, and its most common adverse effects are gastrointestinal (GI). It may produce esophagitis, and even esophageal perforation, if the pill were to get caught in the esophagus while swallowing. For that reason, patients taking alendronate are instructed to take it on an empty stomach with a full glass of water and to remain upright for at least 30 minutes after ingesting the medication.

APPROACH TO:
Pharmacology of Agents Regulating Calcium Homeostatis

OBJECTIVES

1. Know the structure, actions, and uses of PTH.
2. Describe the structure, actions, and uses of calcitonin (CT).

3. Describe the structure, synthesis, actions, and uses of vitamin D and its metabolites.
4. Know the secondary agents that affect calcium homeostasis and their characteristics.

DEFINITIONS

Osteocyte: A bone-maintaining cell, an embedded osteoblast.

Osteoblast: Bone-forming cells derived from the stroma of bone.

Osteoclast: Bone-resorptive cell derived from myeloid lineages.

OPG (osteoprotegerin): A member of the OPG, OPGL (osteoprotegerin ligand), RANK (receptor activator of nuclear factor-κB) signal transduction cascade that is central to bone metabolism.

DISCUSSION

Class

Calcium is the major extracellular divalent ion. It has diverse roles—including enzyme activation, secretion, excitation-contraction coupling in all muscle types, and neuronal function—and is a critical structural element in bone and teeth.

Approximately **40–50 percent of serum calcium exists as free, ionized Ca^{2+}.** This is **the biologically active fraction,** and it is maintained at approximately 2.5 mM in the serum. An additional **40 percent is bound to serum proteins** and the remainder is complexed to ions such as phosphate, citrate, and bicarbonate. The serum concentration of $Ca^{2+}$is tightly regulated by several endocrine systems and three major tissues: the **gut, kidney, and bone.**

Bone is the **storage depot** for over **99 percent of calcium in the body,** and most of the calcium is in the form of **hydroxyapatite:** $[Ca_{10}(PO_4)_6(OH)_2]$. Bone is a remarkably dynamic tissue and bone remodeling is a continuous process. Normal bone is continuously **reabsorbed by the action of osteoclasts,** and **new bone is formed by the action of osteoblasts;** if these two processes are not equal in magnitude, excess bone can be lost, as in osteoporosis, or too much bone can be formed. **Coupling of the actions of osteoblasts and osteoclasts is largely under the control of the OPG/RANKL signaling system** (Figures 44–1A and 44–1B).

Osteoblasts produce **RANKL,** a polypeptide that binds to receptors on osteoclasts termed **RANK-R,** a member of the TNF receptor family**. Stimulation of RANK-R** leads to increased **proliferation, maturation, and activation** of **osteoclasts. Osteoblasts** also elaborate **osteoprotegerin,** which is a **molecular antagonist of RANKL.** OPG can bind RANKL before it can activate the RANK-R on osteoclasts. Osteoclast activation is thus controlled by the ratio of OPG/RANKL that is secreted by osteoblasts. Most drugs that act to alter calcium homeostasis in bone do so by altering OPG/RANKL. Many cytokines and hormones such as estradiol and PTH alter bone metabolism by changing OPG/RANKL.

PTH is an 84-amino acid peptide synthesized in the **parathyroid glands** and is **secreted in response to low serum-ionized Ca^{2+}**. PTH 1–34, the *N*-terminal portion of PTH, has full biologic activity. In the **kidney it acts to increase Ca^{2+} reabsorption** and **promotes phosphate ($PO4^{2-}$) excretion.** It has indirect effects on the **GI** system

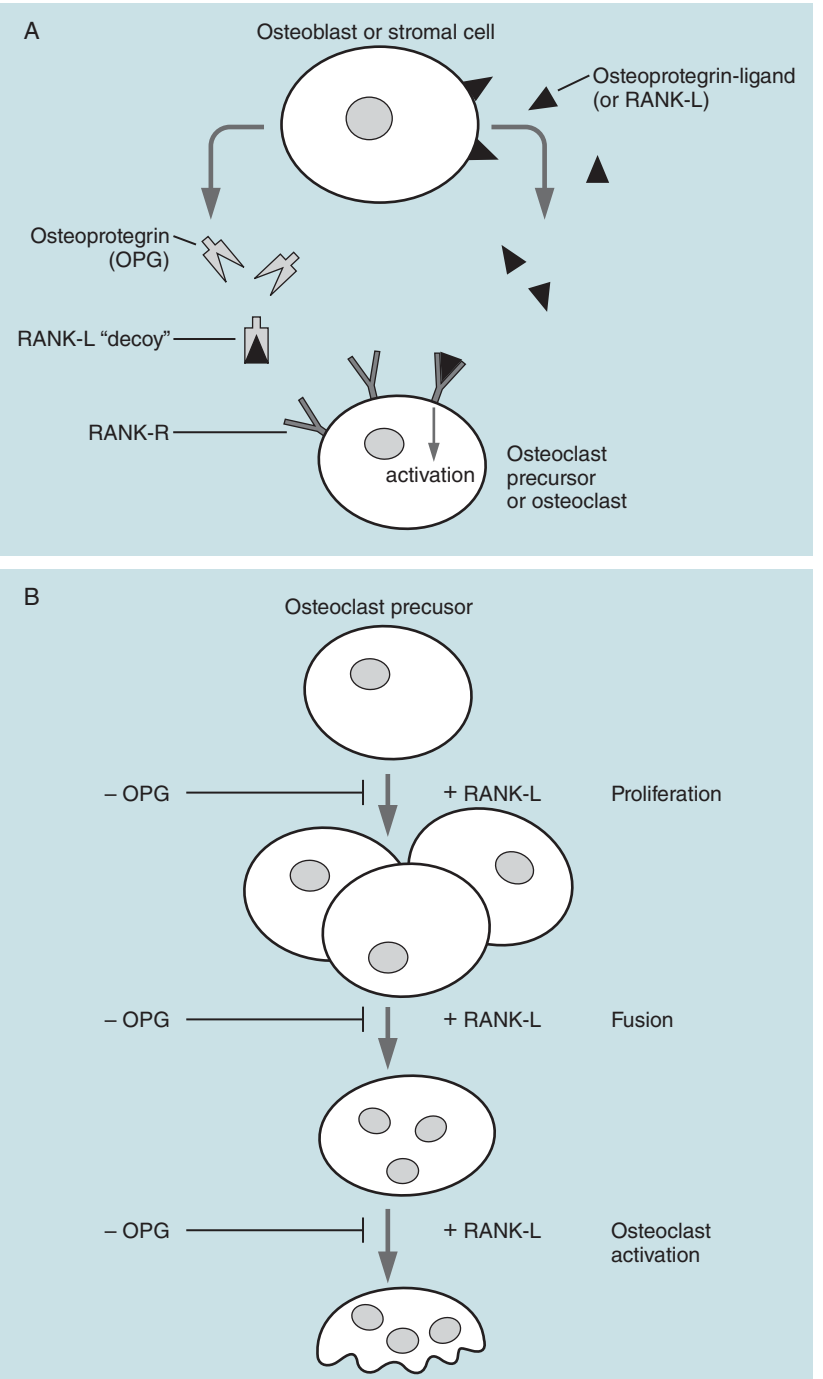

Figure 44–1. Osteoblast (A) and osteoclast (B). The OPG/RANKL-signaling system controls the number and activity of osteoclasts. Osteoblasts secrete both OPG and RANKL. Activation of RANK-R by RANKL stimulates proliferation and activation of osteoclasts. OPG is a "decoy" that binds RANKL in the interstitial space and prevents its association with its receptor (RANK-R).

to **increase Ca^{2+} absorption by stimulating vitamin D production.** The effects of PTH on bone are complex and dependent on the temporal nature of its release or administration.

Continuously elevated PTH, as in hyper-parathyroidism, increases osteoclast activity via increased RANKL and results in increased bone resorption. Pulsatile release of PTH activates **osteoblasts** and increases bone formation.

CT is a 32-amino acid polypeptide produced in the **parafollicular cells** of the **thyroid.** It is secreted in response to elevated serum Ca^{2+} levels. **CT increases OPG and decreases RANKL release** from **osteoblasts,** and its action on bone is to **reduce bone turnover.** In response to CT, osteoclasts withdraw reabsorptive processes, shrink in size, and retract the ruffled border from the surface of bone; CT effectively prevents all stages of osteoclastic bone resorption. It **increases renal excretion of Ca^{2+}, $PO4^{2-}$, Mg^{2+}, Cl^{-}, and K^{+} by decreasing reabsorption of these ions.**

The **third endocrine system** that has effects on **bone** is **vitamin D_3** and its **metabolites.** Vitamin D_3 (not a true vitamin in a nutritional sense) is a **prehormone** that undergoes a series of metabolic alterations to the final agonist in the pathway, 1,25-$(OH)_2$ vitamin D_3. **Vitamin D_3 is synthesized from cholesterol** in the skin in a **two-step photo-dependent reaction.** Vitamin D_3 is converted by the **liver enzyme 25-hydroxylase to 25-(OH) D_3;** in the **kidney** the enzyme **1-hydroxylase metabolizes 25-(OH) D_3 to 1,25-$(OH)_2$ D_3. 1,25-$(OH)_2$ D_3** acts on the intestine to **increase intestinal absorption of Ca^{2+}.** In the **kidney,** 1,25-$(OH)_2$ D_3 acts to **increase the absorption** of both **Ca^{2+}** and **$PO4^{2-}$.** 1,25-$(OH)_2$ D_3 stimulates Ca^{2+} mobilization from bone and enhances the resorptive action of PTH on bone. However, **1,25-$(OH)_2$ D_3** also induces **osteocalcin** and **osteopontin, two matrix proteins** important in bone formation.

Treatment of Hypocalcemia

Calcium Salts A wide variety of preparations are available for both IV and oral administration for treating **acute hypocalcemic tetany.** These include **calcium gluconate, calcium lactate, calcium carbonate, and calcium citrate.** They vary in the percentage of calcium by weight from a low of 9 percent for calcium gluconate to a high of 40 percent for calcium carbonate.

Vitamin D Several vitamin D or vitamin D-related agents are available for use for hypocalcemia and osteoporosis (Table 44–1). Selection of which agent to use depends on the desired onset of action, duration of effect, and the presence of underlying liver or kidney disease. Thiazide diuretics act on the kidney to increase Ca^{2+} reabsorption in the distal convoluted tubule and can be used in the treatment of hypocalcemia.

Treatment of Hypercalcemia **Hypercalcemia** has a number of pathophysiologic causes including **hyperparathyroidism, Paget disease, and hypercalcemia of malignancy. CT** is useful for **short-term treatment of hypercalcemia.** Salmon CT is more potent and has a longer half-life than human CT and is the form used therapeutically. CT has few side effects but **refractoriness** frequently develops. CT is available for parenteral and nasal administration. Peak plasma concentration after an inhaled

Table 44–1 • VITAMIN D-RELATED AGENTS

Agent	Chemical Nature	Time to Maximum Effect	Duration of Action	Requirement for Metabolism
Cholecalciferol	Vitamin D_3	4 weeks	8 weeks	Liver, kidney
Ergocalciferol	Vitamin D_2	4 weeks	8 weeks	Liver, kidney
Dihydrotachysterol	1-(OH) D_3	1-2 weeks	1-2 weeks	Liver
Doxercalciferol	1-(OH) D_2	1-2 weeks	1-2 weeks	Liver
Calcifediol	25-(OH) D_3	2-3 weeks	2-3 weeks	Kidney
Paricalcitol	25-(OH) D_2	2-3 weeks	2-3 weeks	Kidney
Calcitriol	1,25-$(OH)_2$	D_3 24 hours	3-5 days	None

dose is approximately 30 minutes after administration, but normalization of the rate of bone turnover as in Paget disease may take several months.

Bisphosphonates are **analogs of pyrophosphate in which the phosphodiester (P-O-P) bond is replaced by a nonhydrolyzable bisphosphonate (P-C-P) bond.** First-generation bisphosphonates included sodium **etidronate.** Second-generation aminobisphosphonates include **risedronate, alendronate, pamidronate, tiludronate, clodronate, zoledronate, and ibandronate.** The two classes of bisphosphonates have different mechanisms of action and different potencies. For example, **risedronate** is 1000 times more potent as an inhibitor of bone resorption than etidronate. All bisphosphonates bind to and accumulate in bone, and this provides a measure of tissue specificity. The first-generation nonnitrogenous bisphosphonates are converted into an adenosine triphosphate (ATP) analog that cannot be internalized. This metabolite impairs osteoclast function and triggers osteoclast apoptosis. The aminobisphosphonates are not converted into an ATP analog; rather they interfere with mevalonate and ubiquitin metabolism (similar to statins). This leads to impaired posttranslational modification of a number of proteins that are critical to osteoclast function. Ultimately, the aminobisphosphonates lead to osteoclast hypofunction. **Etidronate** is available for oral use; the aminobisphosphonates may be administered orally or by infusion. Administered orally, all the bisphosphonates have **very poor (approximately 5%) bioavailability,** but sufficient drug is absorbed to achieve therapeutic concentrations in bone. All bisphosphonates are approved for treatment of **Paget disease; alendronate,** risendronate, zoledronate, and ibandronate are also approved for **prevention and treatment of osteoporosis** (pamidronate is approved for treatment of osteoporosis). The remaining aminobisphosphonates are used to treat hypercalcemia of malignancy. Adverse effects of bisphosphonates include **GI upset, diarrhea, and nausea.** Bisphosphonates are associated with **lower esophageal erosion,** and the recommendation with alendronate and risedronate is to **avoid lying down for 30 minutes after oral administration to avoid reflux.** There have been reports of bisphosphonate use associated with the osteonecrosis of the jaw. Although rare, this seems to occur most often in cancer patients receiving bisphosphonate therapy.

Loop diuretics increase the amount of Ca^{2+}excreted and can be used in the acute management of hypercalcemia.

Treatment of Osteoporosis **Osteoporosis,** loss of bone mass, affects nearly 30 percent of women aged 65 years and older and a smaller but significant percentage of men. Historically, osteoporosis has been divided into **postmenopausal osteoporosis,** which occurs in women and is related to the loss of ovarian hormones after menopause, and **senile osteoporosis,** which is age related and affects both sexes. Histologically and biochemically, they seem indistinguishable disorders of bone metabolism caused by excessive bone reabsorption or inadequate bone formation. Adequate dietary Ca^{2+} and vitamin D (to facilitate Ca^{2+} absorption) is critical in patients at risk for osteoporosis. The recommended daily allowance (RDA) for Ca^{2+}in patients at risk is **1200 to 1500 mg/day.**

Teriparatide (PTH 1–34) has been approved for the treatment of osteoporosis. Administered intermittently, once a day by injection, teriparatide **increases bone formation in excess of resorption.** This treatment has been shown to increase bone mass and decrease the incidence of fractures. Studies in **rats** receiving very high doses of teriparatide for 2 years demonstrated an **increased frequency of osteosarcoma.** It is **contraindicated in patients with bone malignancy or in pediatric patients.** Major adverse effects are **hypotension, hypocalcemia, dizziness, and nausea.**

Estrogens (see Case 40) have been shown to reduce the rate of bone loss in the postmenopausal period when the rate of loss can be as high as 10 percent per year. Estrogens increase bone mineral density and decrease the incidence of vertebral and nonvertebral fractures. However, estrogens do not increase net bone formation.

Selective estrogen receptor modifiers (SERMs) are compounds whose estrogenic activities are tissue selective. Three SERMs are currently approved for use: **tamoxifen, raloxifene, and toremifene. Raloxifene** is approved for the prevention and treatment of osteoporosis; tamoxifen and toremifene are used to treat breast cancer. Raloxifene is a polyhydroxylated nonsteroidal compound that binds to the estrogen receptor, but it has estrogen-agonist activity only in bone and the liver; it has no effect on the uterus, and it is an estrogen antagonist in breast tissue and in the brain. It has antiresorptive activity in bone. It increases bone mineral density and has been shown to decrease the incidence of vertebral and nonvertebral fractures. Adverse effects include hot flashes and leg cramps. More serious adverse effects include an approximate threefold increase in deep vein thrombosis and pulmonary embolism.

Denosumab is a monoclonal **antibody against RANKL.** It is approved for use in postmenopausal women at high risk of fracture. It is also approved as a treatment to increase bone mass in patients who are at high risk of fracture from receiving androgen deprivation therapy for nonmetastatic prostate cancer or aromatase inhibitor (AI) therapy for breast cancer. In men with nonmetastatic prostate cancer, denosumab reduced the incidence of vertebral fracture.

Sodium fluoride has been examined in a number of clinical trials for the treatment of osteoporosis. Early studies using relatively high doses reported an increase in bone mineral density but no decrease in the incidence of fractures, probably because of the formation of abnormal hydroxylapatite crystals in bone. More recent studies

using slow-release monofluoride have suggested a decrease in fracture rates, but fluoride is not yet approved for the treatment of osteoporosis.

COMPREHENSION QUESTIONS

44.1 Which of the following vitamin D preparations would be the most appropriate in a patient with poor renal function?

A. Calcifediol
B. Calcitriol
C. Cholecalciferol
D. Ergocalciferol

44.2 Intermittent administration of PTH produces which of the following?

A. Impaired Ca^{2+} absorption in the gut
B. Inhibition of 1-hydroxylase
C. Net increase in bone formation
D. Net increase in bone resorption

44.3 A 53-year-old woman who is being treated for metastatic breast cancer is noted to have some lethargy, fatigue, and an elevated serum calcium level. She is brought into the emergency department for near comatose state, thought to be caused by the hypercalcemia. After addressing the ABCs (airway, breathing, circulation), which of the following is the best therapy for this patient?

A. Bisphosphonates
B. CT
C. IV estrogen therapy
D. Saline infusion and furosemide

44.4 A postmenopausal women with a family history of osteoporosis completes a bone mineral density work-up and you find her T-score is –2.6. She tried a short course of teriparitide a year ago but complained of serious depression and mood changes. You elect to try an antibody-based therapy and schedule a time for an injection. Which of the following is the drug you have selected?

A. Calcitonin
B. Dihydrotachysterol
C. Denusomab
D. Infliximab

ANSWERS

44.1 **B.** 1-Hydroxylase activity must be adequate to produce $1,25(OH)_2\ D_3$. Calcitriol is the only choice that is already 1-hydroxylated.

44.2 **C.** Intermittent administration of PTH on its analogs will result in bone formation. Continuous dosing or a PTH-secreting tumor will cause bone resorption.

44.3 **D.** Loop diuretics, given with IV normal saline, are the best choice in a patient with acute-onset hypercalcemia.

44.4 **C.** Denosumab is an antibody against RANLK. It blocks proliferation and activation of osteoclasts and is administered every 6 months by SQ injection. Calcitonin is not very effective in osteoporosis, DHT is a vitamin D analog. Inflizimab is an anti-TNF antibody used for RA and IBS.

PHARMACOLOGY PEARLS

- Teriparatide (PTH 1–34) is the only agent on the market that promotes new bone formation.
- Estrogens slow the rate of resorption but do not increase bone formation.
- Thiazide diuretics promote renal reabsorption of Ca^{2+}; loop diuretics have the opposite effect.
- Bisphosphonates can lead to severe esophageal erosions; patients are advised to not lie down for 30 minutes after taking them.

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CASE 45

A 22-year-old woman enters your clinic with the chief complaint of irregular menstrual periods. She indicates that she was 14 when her periods first started and that they had never really been very regular. On physical examination she is 5′4″ and weighs 195 lb. She has mild acne on her face and shoulders and a more-than-normal amount of facial hair. There is a darkening of the skin at the base of her neck and across her shoulders. Blood tests reveal an elevated LH and a normal FSH level (LH/FSH 3.2). You suspect she may have polycystic ovary syndrome (PCOS) and start her on metformin.

- What is the effect of insulin on the ovaries?
- What is the mechanism of action of metformin?

ANSWERS TO CASE 45:
Agents for the Treatment of PCOS

Summary: A 22-year-old woman with obesity, hirsutism, and irregular menstrual cycles, consistent with the diagnosis of PCOS.

- **Effect of insulin on the ovaries:** Insulin stimulates steroidogenesis, especially androgen production within the ovary.
- **Mechanism of action of metformin:** Metformin activates AMP kinase; this central regulator of metabolism acts to increase glucose uptake and metabolism in skeletal muscle and decrease glucose production in the liver.

CLINICAL CORRELATIONS

PCOS is a very common cause of irregular menstrual periods and infertility. It is frequently associated with obesity and the concomitant insulin resistance and hyperinsulinemia. The excessive insulin increases production of ovarian androgens such as androstenedione and dehydroepiandrosterone, which can act peripherally and increase both sebum production and hair growth. Acanthosis nigricans (darkened shoulders) is a manifestation of hyperinsulinemia. Metformin is an oral antidiabetic agent that causes metabolic changes that decrease serum glucose and insulin levels.

APPROACH TO:
PCOS

OBJECTIVES

1. Know the agents for the treatment of PCOS.
2. Know the mechanism of action, uses, and adverse effects of the agents.

DEFINITIONS

PCOS: Polycystic ovary syndrome (also known as Stein-Leventhal syndrome or polycystic ovary disease [PCOD]) is one of the leading causes of infertility in women.

Acanthosis nigricans: A velvety darkening of the skin commonly seen at the nape of the neck, elbows, axilla, and knuckles usually caused by hyperinsulinemia.

DISCUSSION

PCOS is characterized by a lack of regular ovulation and excessive amounts or effects of androgenic (masculinizing) hormones. The ovaries accumulate benign cysts produced by abnormal follicular development and lack of ovulation due to endocrine dysfunction. Patients with PCOS tend to have high body mass index (BMI),

glucose intolerance, and insulin resistance. The elevated insulin level due to the insulin resistance is a potent stimulator of steroidogenesis, especially of androgens, in the ovary. The androgens cause acne and hirsutism, both frequently associated with PCOS. Hyperinsulinemia increases GnRH pulse frequency, LH over FSH dominance, decreased follicular maturation, and decreased sex hormone–binding globulin; all these steps contribute to the development of PCOS.

Metformin is a biguanide oral antihyperglycemic agent. It appears to act by activating AMP kinase, an important metabolic integrator with effects on adipose tissue, skeletal muscle, cardiac muscle, liver, and hypothalamus. Activation of AMP kinase reduces glycogen production, reduces fatty acid oxidation, and facilitates glucose uptake.

In PCOS patients, metformin reduces insulin resistance and lowers insulin levels, which lowers serum androgen concentrations, restores normal menstrual cycles and ovulation, and may help to resolve PCOS-associated infertility. Metformin, when administered to lean, overweight, and moderately obese women with PCOS, has been found to significantly reduce serum luteinizing hormone (LH) and increase FSH and sex hormone–binding globulin (SHBG). Serum testosterone concentrations were also found to decrease by approximately 50 percent.

GI adverse effects are seen in approximately 30 percent of patients taking metformin. GI effects include anorexia, nausea/vomiting, abdominal discomfort, dyspepsia, flatulence, diarrhea, and dysgeusia (metallic taste). These side effects tend to decline with continued use and can be minimized by initiating therapy with low doses of metformin. Asymptomatic vitamin B_{12} deficiency was reported with metformin monotherapy in 9 percent of patients during clinical trials. The risk of hypoglycemia is much less common with metformin than with the sulfonylureas.

Other agents that are used to treat PCOS include oral contraceptives, which reduce LH and ovarian androgen production and finasteride, a potent 5α-reductase inhibitor (see Case 40). In PCOS patients desiring to become pregnant, clomiphene induces ovulation in about 45 percent. In patients unsuccessfully treated with clomiphene alone, addition of metformin may increase the ovulation and conception rates.

COMPREHENSION QUESTIONS

45.1 Which of the following would be the best agent to use in a patient with PCOS?

A. Pioglitazone
B. Metformin
C. Regular insulin
D. Repaglinide

45.2 Which of the following is the most common adverse effect of metformin?

A. Hypoglycemia
B. Hyperinsulinemia
C. GI effects
D. Pruritis

45.3 Which of the following is the mechanism of action of metformin?

A. Increase insulin secretion by the pancreas
B. Increase hepatic sensitivity to insulin
C. Reduction in DHT production
D. Increased muscle uptake of glucose

ANSWERS

45.1 **B**. Pioglitozone, as an insulin sensitizer, might be efficacious in the treatment of PCOS but metformin has fewer and less severe side effects. Repaglinide stimulates insulin secretion, which would be detrimental in PCOS.

45.2 **C**. Metformin infrequently causes hypoglycemia and hypersensitivity reactions, for instance in the skin, are rare.

45.3 **D**. Metformin does not increase insulin production; it appears to act by decreasing plasma glucose by affecting metabolism rather than altering the sensitivity of tissues to insulin.

PHARMACOLOGY PEARLS

- Metformin reduces insulin levels and can improve insulin sensitivity without weight gain.
- Metformin rarely causes hypoglycemia.

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CASE 46

A 48-year-old man comes to your office with a 6-day history of worsening cough productive of green sputum. He has had fever and chills. He complains of pain in the right midback with deep breathing or coughing. Further history reveals that he has smoked one pack of cigarettes a day for 30 years. He has no other significant medical history. On examination, his temperature is 38.1°C (100.5°F); his respiratory rate is 24 breaths per minute; pulse, 98 beats per minute; blood pressure, 120/75 mm Hg; and saturation of oxygen, 96 percent on room air by pulse oximetry. Auscultation of his lungs reveals rales in the right lower-posterior lung field. The remainder of his examination is within normal limits. A posterior-to-anterior (PA) and lateral chest x-ray show a right lower-lobe infiltrate. A sputum Gram stain reveals gram-positive cocci, and subsequent sputum and blood culture results confirm the diagnosis of pneumonia caused by *Streptococcus pneumoniae* (pneumococcus). You treat him with a combination of amoxicillin and clavulanic acid.

- What is the mechanism of action of amoxicillin?
- What is the mechanism of action of clavulanic acid?

ANSWERS TO CASE 46:
Antibacterial Agents

Summary: A 48-year-old man with pneumococcal pneumonia is being treated with amoxicillin and clavulanic acid.

- **Mechanism of action of amoxicillin:** Inactivation of bacterial transpeptidases and prevention of cross-linking of peptidoglycan polymers necessary for cell-wall integrity, resulting in loss of cell-wall rigidity and cell rupture; also inhibition of cell-wall synthesis.
- **Mechanism of action of clavulanic acid:** Irreversible inhibition of β-lactamase.

CLINICAL CORRELATION

Penicillin is the prototype antibiotic in the β-lactam class. **β-Lactam antibiotics interfere with bacterial transpeptidases** and thereby **prevent the cross-linking of peptidoglycan** polymers essential for **cell-wall integrity.** They do this by binding to the active site of the penicillin-binding protein (an enzyme) that is involved in maintaining cell-wall stability. β-Lactam antibiotics are **bactericidal** in growing cells, with gram-positive bacteria being particularly susceptible. Penicillin has activity against many gram-positive aerobic organisms, some gram-negative aerobes and anaerobic organisms. It does not have significant activity against gram-negative rods. Amoxicillin is an extended-spectrum penicillin with better activity against gram-negative rods and similar activity against other organisms. **Both penicillin and amoxicillin are susceptible to β-lactamases,** which cleave the β-lactam ring required for antibacterial action. Clavulanic acid (and sulbactam and tazobactam) is structurally similar to penicillin. It has no antimicrobial activity of its own but it irreversibly inhibits certain β-lactamases. It frequently is given in fixed combination with amoxicillin, thus allowing it to be used to treat β-lactamase-producing organisms. Penicillins can cause hypersensitivity reactions in susceptible persons. Approximately 5 to 10 percent of penicillin-allergic persons will have a cross-sensitivity to cephalosporin drugs as well. Penicillins also have gastrointestinal (GI) side effects, and the addition of clavulanic acid significantly increases the incidence of diarrhea. Although antibiotic resistance should be considered in the choice of antibiotic therapy in streptococcal pneumonia, the incidence of resistance is declining due to the availability of a vaccine routinely given to children.

APPROACH TO:

Pharmacology of Antibacterial Agents

OBJECTIVES

1. Describe the factors in choosing appropriate antibiotic agents.
2. List the classes of antibiotics, and describe their mechanisms of action, therapeutic uses, and adverse effects.
3. Outline mechanism of development of bacterial drug resistance.

DEFINITIONS

Plasmids: Extrachromosomal genetic elements that may be transferred between bacteria.

Bactericidal antibiotics: Kill bacteria.

Bacteriostatic antibiotics: Prevent the growth of bacteria.

DISCUSSION

Class

The basic principles for the selection of **antibacterial therapy** include consideration of factors such as the **likelihood that the infection is bacterial** and the identification of the **likely infecting organism** to support a rational selection of an antibiotic (Table 46–1). Consideration of host and drug factors that could influence antibiotic selection include identification of the site of infection, which will influence the selection of the antibiotic and its route of administration; recognition of concomitant diseases such as AIDS; recognition of the likelihood of drug allergies; recognition of hepatic or renal dysfunction that could alter antibiotic clearance; and recognition of drug toxicity, drug-drug interactions, drug resistance, the patient's age or pregnancy or maternal status; and drug cost.

Antibacterial agents, which target specific components of microorganisms that are unique or more essential to their function than they are to humans, are classified according to their mechanisms of action. The component targets include **enzymes necessary for bacterial cell-wall synthesis, the bacterial ribosome, and enzymes necessary for nucleotide synthesis and deoxyribonucleic acid (DNA) replication.**

Resistance of pathogens to antibacterial and other chemotherapeutic agents may be the result of a natural resistance or may be acquired. In either case, it occurs through mutation, adaptation, or gene transfer. The mechanism of resistance for any antibacterial agent varies, but is a result of either changes in uptake of drug into, or its removal from, the bacterial cell, or to changes in the bacterial cell target site of the drug from a gene mutation. **Multiple drug resistance** is also a major impediment to antibacterial therapy and may be **chromosomal or plasmid mediated,** where genetic elements from resistant bacteria that code for enzymes that inactivate antibacterial agents are transferred to nonresistant bacteria. The emergence of drug

Table 46–1 • ANTIBIOTIC DRUG TARGETS*						
Antibiotic Class	**Representative Drug**	**Effective against Gram Positive?**	**Effective against Gram Negative?**	**Effective against Pseudomonas?**	**Effective against MRSA?**	**Effective against Anaerobes?**
Aminoglycides	Gentamicin	No	**Yes**	**Yes**	No	No
Carbapenem	Imipenem	**Yes**	**Yes**	**Yes**	No	**Yes**
1st Generation cephalosporins	Cefalexin	**Yes**	No	No	No	**Yes**
2nd Generation cephalosporins	Cefuroxime	**Yes**	**Yes**	No	No	**Yes**
3rd Generation cephalosporins	Ceftriaxone	**Yes**	**Yes**	No	No	**Yes**
4th Generation cephalosporins	Cefepime	**Yes**	**Yes**	**Yes**	No	No
5th Generation cephalosporins	Cetaroline	**Yes**	**Yes**	No	**Yes**	No
Glycopeptides	Vancomycin	**Yes**	No	No	**Yes**	**Yes**
Lincosamides	Clindamycin	**Yes**	No	No	**Yes**	**Yes**
Macrolides	Azithromycin	**Yes**	**Yes**	No	No	No
Monobactams	Aztreonam	No	**Yes**	**Yes**	No	No
Nitrofurans	Nitrofurantoin	**Yes**	**Yes**	No	No	No
Penicillins	Amoxicillin	**Yes**	**Yes**	No	No	**Yes**
Fluroquinolones	Ciprofloxacin	**Yes**	**Yes**	**Yes**	No	No
Sulfonamides	Sulfamethoxazole	**Yes**	**Yes**	No	**Yes**	No
Tetracyclines	Doxcycline	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**

*This is a guide only. Whenever possible antibiotic choices should be guided by a culture and susceptibility results.

Table 46–2 • PARTIAL LISTING OF PENICILLINS

Natural Penicillin G (prototype) Penicillin V	*Extended-Spectrum Aminopenicillins* Ampicillin Amoxicillin *Ureidopenicillins* Mezlocillin Piperacillin *Carboxypenicillin* Ticarcillin
β-Lactamase Resistant Nafcillin Oxacillin Cloxacillin Dicloxacillin	

resistance is to a large degree the result of the widespread and often unnecessary or inappropriate use of antibiotics in humans.

The **penicillins** (see above) include natural penicillins, penicillins that are resistant to staphylococcal β-lactamase, and extended-spectrum penicillins (Table 46–2).

The **cephalosporins** are classified as first to fifth generation, according to their antibacterial spectrum (Table 46–3).

Table 46–4 lists these and other selected antimicrobial agents. **Aztreonam,** which is relatively β-lactamase resistant, is the only available monobactam. It is nonallergenic and is active only against aerobic gram-negative bacilli (eg, pseudomonas, serratia). The **carbapenems** (imipenem, meropenem, and ertapenem), which are resistant to most β-lactamases, have a wide spectrum of activity against gram-positive and gram-negative rods and anaerobes. To **prevent its metabolism, imipenem** is administered with an **inhibitor of renal tubule dehydropeptidase, cilastatin.**

Table 46–3 • SELECTED LISTING OF CEPHALOSPORINS REPRESENTATIVE

Cephalosporins (Route)	Notes
First Generation • Cefazolin (IV) • Cephalexin (PO) • Cefadroxil (PO)	Active against gram-positive cocci, including staphylococci, pneumococci, and streptococci. They are particularly good for soft tissue and skin infection
Second Generation • Cefuroxime (IV) oral form is cefuroxime axetil • Cefotoxin (IV) • Cefotetan (IV)	These agents have marked differences in their spectrum of activity. In general, they are active against certain aerobic gram-negative bacteria in addition to activity against many gram-positive organisms sensitive to first-generation cephalosporins. Certain agents are active against *Haemophilus influenza* (eg, cefuroxime), whereas others are active against *Bacteroides fragilis* (eg, cefotoxin)
Third Generation • Cefotaxime (IV) • Ceftazidime (IV) • Ceftriaxone (IV)	Expanded aerobic gram-negative spectrum. Cross the blood-brain barrier. Useful to treat bacterial strains resistant to other drugs
Fourth Generation • Cefepime (IV)	Generally similar activity to third-generation cephalosporins but more resistance to β-lactamases Also has pseudomonal coverage
Fifth Generation • Ceftaroline • Ceftobiprole	Effective against gram positive and MRSA

Table 46–4 • PARTIAL LISTING OF ANTIMICROBIAL AGENTS

Antibacterial Agents	Mechanism of Action	Adverse Effects
β-Lactam antibiotics Penicillins Cephalosporins Monobactams • Aztreonam (p) *Carbapenems* • Imipenem (p) • Meropenem (p) • Ertapenem (p) *Vancomycin* (o,p)	Inhibit synthesis of the bacterial cell wall Bactericidal	*β-Lactam antibiotics:* hyper-sensitivity with rare potential for anaphylactic shock *Cephalosporins:* may cause local irritation and pain from IM injection. Those with a methylthiotetrazole group, eg, cefotetan, may cause hypoprothrombinemia and bleeding disorders *Aztreonam:* occasionally may cause skin rashes *Carbapenems:* may cause GI discomfort and skin rashes and seizures in patients with renal dysfunction (particularly imipenem) *Vancomycin:* relatively nontoxic. Fever, chills, and infusion-related flushing ("red-man" syndrome) are encountered. Ototoxicity is a rare effect
Chloramphenicol *tetracyclines* • Tetracycline (o,p) • Oxytetracycline (o,p) • Doxycycline (o,p) • Methacycline (o) • Minocycline (o,p) *Macrolides* • Erythromycin (o,p) • Clarithromycin (o) • Azithromycin (o) *Ketolides* • Telithromycin (o) *Oxazolidinones* • Linezolid (o,p) *Aminoglycosides* • Streptomycin (p) • Neomycin (o) • Amikacin (p) • Gentamicin (p) • Tobramycin (p,i) *Spectinomycin (p)* *Lincomycins* • Clindamycin (o,p)	Bind to bacterial ribosomes to inhibit protein synthesis Bacteriostatic	*Chloramphenicol:* GI disturbances, reversible suppression of bone marrow, rarely aplastic anemia *Tetracyclines:* GI disturbances and bacterial overgrowth, teeth and bone deformation in children *Erythromycin and clarithromycin:* severe GI disturbances, hypersensitivity, hepatic P450 inhibition. *Telithromycin:* hepatic P450 inhibition *Linezolid:* reversible thrombocytopenia *Aminoglycosides:* ototoxicity and nephrotoxicity *Clindamycin:* GI disturbances, hepatic dysfunction, potentially fatal colitis

(*Continued*)

Table 46–4 • PARTIAL LISTING OF ANTIMICROBIAL AGENTS (CONTINUED)

Antibacterial Agents	Mechanism of Action	Adverse Effects
Sulfonamides • Sulfadiazine (o) • Sulfamethizole (o) • Sulfamethoxazole (o) • Sulfanilamide (t) • Sulfisoxazole (t,o) *Trimethoprim*	*Sulfonamides:* structural analogs of p-aminobenzoic acid that inhibit bacterial dihydropteroate synthase to block folic acid synthesis and cell growth *Trimethoprim:* selectively inhibits dihydrofolic acid reductase to block folic acid synthesis and cell growth. Acts synergistically with sulfamethoxazole with which it is often coadministered Bacteriostatic	*Sulfonamides:* hypersensitivity urinary tract dysfunction, hemolytic or aplastic anemia, potentially fatal Stevens-Johnson syndrome *Trimethoprim:* blood dyscrasias
Fluoroquinolones (selected) • Ciprofloxacin (t,o,p) • Levofloxacin (t,o,p) • Ofloxacin (t,o,p) • Moxifloxacin (o,p)	Inhibit activity of bacterial topoisomerase (DNA gyrase) that is necessary for replication Bactericidal	GI disturbances, reversible arthropathy, arrhythmias, tendon rupture

t = topical, o = oral, p = parenteral, i = inhalation.

Vancomycin, which is unaffected by β-lactamases, **inhibits bacterial cell-wall synthesis** by covalent binding to the terminal two D-alanine residues of nascent peptidoglycan pentapeptide to prevent their elongation and cross-linking, thus increasing the susceptibility of the cell to lysis. It is **active against gram-positive bacteria.**

COMPREHENSION QUESTIONS

46.1 Which of the following is the most likely explanation for multiple drug resistance to antibiotics that spreads from one type of bacteria to another?

A. Adaptation
B. Decreased bioavailability
C. Gene transfer
D. Mutation

46.2 Penicillins inhibit which of the following bacterial processes/compounds?

A. Protein synthesis
B. Topoisomerase
C. Dihydropteroate synthase
D. Cell-wall synthesis

46.3 Ototoxicity and nephrotoxicity are characteristic adverse effects of which of the following?

A. Aminoglycosides
B. β-Lactam antibiotics
C. Chloramphenicol
D. Fluoroquinolones

ANSWERS

46.1 **C.** Antibiotic drug resistance can occur through bacterial cell mutation, adaptation, or gene transfer. The best route for multiple drug resistance that spreads from one type of bacteria to another is via plasmid or chromosomal gene transfer.

46.2 **D.** Penicillins inhibit synthesis of the bacterial cell wall. Chloramphenicol, tetracyclines, macrolides, ketolides, oxazolidinones, aminoglycosides, spectinomycin, and the lincomycin bind to bacterial ribosomes to inhibit protein synthesis. The fluoroquinolones inhibit activity of bacterial topoisomerase to inhibit protein synthesis, and the sulfonamides inhibit bacterial dihydropteroate synthase to block folic acid synthesis and cell growth.

46.3 **A.** Ototoxicity and nephrotoxicity are characteristic adverse effects of aminoglycosides. Chloramphenicol can cause GI disturbances, reversible suppression of bone marrow, and rarely aplastic anemia. As a group, the β-lactam antibiotics can cause hypersensitivity and have the potential to cause anaphylactic shock. The fluoroquinolones can cause GI disturbances, reversible arthropathy, and arrhythmias.

PHARMACOLOGY PEARLS

- β-Lactam antibiotics inactivate bacterial transpeptidases and prevent the cross-linking of peptidoglycan polymers essential for cell-wall integrity.
- Both penicillin and amoxicillin are susceptible to β-lactamases.
- To prevent its metabolism, imipenem is administered with an inhibitor of renal tubule dehydropeptidase, cilastatin.
- Vancomycin, which is unaffected by β-lactamases, is active against gram-positive bacteria.
- Aminoglycosides may cause ototoxicity or nephrotoxicity and should be used with caution in those patients who have renal insufficiency or who are elderly.

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CASE 47

A 58-year-old man presents for the evaluation of a painful rash. He says that for 2 or 3 days he had a sharp, burning pain radiating from his midback around to his left side. He thought that he was having a kidney stone. Yesterday he noticed a rash that spread in a distribution "like a line" in the same area in which he had the pain. His current medications are glyburide for type II diabetes, simvastatin for high cholesterol, and lisinopril for hypertension, each of which he has been taking for several years. He does have a history of chickenpox as a child. On examination he has a low-grade fever and otherwise normal vital signs. His skin examination is remarkable for a rash in a belt-like distribution from his spine around his left flank to the midline of the abdomen. The rash consists of erythematous patches with clusters of vesicles. The remainder of his examination is normal. You make the diagnosis of herpes zoster and prescribe a course of acyclovir.

- What is the mechanism of action of acyclovir?
- How is acyclovir eliminated from the body?

ANSWERS TO CASE 47:
Antiviral Agents

Summary: A 58-year-old man with herpes zoster is prescribed acyclovir.

- **Mechanism of action of acyclovir:** Purine analog that is converted to a nucleoside triphosphate that competes with the natural triphosphate substrate to inhibit the activity of viral DNA polymerase. It is also incorporated into the growing viral DNA where it acts as a chain terminator. The triphosphate has an increased affinity for viral DNA polymerase compared to native DNA polymerase, which lends specificity to its action.
- **Elimination of acyclovir:** Excreted unmetabolized via the kidney through glomerular and tubular filtration.

CLINICAL CORRELATION

Herpes zoster, also known as shingles, is caused by a reactivation of dormant varicella-zoster virus. It causes a rash and frequently a painful neuropathy, usually in the distribution of a single dermatome. Rarely, Herpes zoster will affect several dermatomes, but should not cross the midline. Acyclovir can shorten the course of symptoms of herpes zoster, although it cannot eradicate latent virus. Acyclovir is a purine analog that is converted to a monophosphate form by a thymidine kinase, which is specific to viruses; this assures its specificity to infected cells. Host cellular enzymes then convert the monophosphate to a triphosphate form that competitively inhibits the activity of viral DNA polymerase. The triphosphate form also is incorporated into viral DNA, where it acts as a chain terminator because the missing 3'-hydroxyl group prevents the further addition of nucleosides. Acyclovir has a low oral bioavailability. It is excreted, largely unchanged, via the kidney. Valacyclovir is a prodrug form of acyclovir that has a greater oral bioavailability than acyclovir. It is rapidly and completely converted to acyclovir after absorption, resulting in higher concentrations of acyclovir.

APPROACH TO:
Pharmacology of Antiviral Drugs

OBJECTIVES

1. List the specific drug classes and drugs used to treat viral disease.
2. Describe the mechanisms of action and adverse effects of antiviral drugs used to treat infections by influenza virus, herpes simplex virus, varicella-zoster virus, cytomegalovirus, human immunodeficiency virus (HIV), and hepatitis C virus.

DISCUSSION

Class

Viral Biology Viruses are obligate intracellular parasites that do not have their own metabolic machinery but rather use the host's metabolic capabilities to replicate. Antiviral medications usually attack the virus prior to cell penetration, after the virus leaves the host cell, or while the virus is active within the host cell. Nonspecific effects may be harmful to the host. Figure 47–1 shows a schematic of the viral life cycle summarized, and Table 47–1 describes specific antiviral therapies aimed at the various viral maturation steps.

There are three main types of viruses: (1) **DNA viruses** usually enter the host cell nucleus and direct the production of new viruses, (2) ribonucleic acid **(RNA) viruses** direct the production of new viruses, usually without entering the host cell nucleus (an exception is influenza), and (3) **RNA retroviruses,** such as HIV. Retroviruses contain an enzyme, reverse transcriptase that makes a DNA copy of the viral RNA; the DNA copy is spliced into the host DNA and directs the production of the new viruses.

Overview of Antiviral Agents The **four major classes of antiviral agents** are (1) **DNA polymerase inhibitors, (2) reverse transcriptase inhibitors, (3) protease inhibitors, and (4) fusion inhibitors.** It should be noted that HIV treatment usually includes the use of three to four antiretroviral agents as standard of care. DNA polymerase inhibitors are categorized as nucleoside or nonnucleoside. Drugs may target viral nucleic acid replication such as DNA polymerase either via nucleoside (purine or pyrimidine analogs), such as acyclovir or ribavirin, or by attacking a unique viral process needed in nucleic acid synthesis, such as viral pyrophosphate (nonnucleoside type).

Antiviral drugs used to treat herpes simplex virus, varicella-zoster virus, and cytomegalovirus can be classified as either nucleoside or nonnucleoside, or according to their site of action in the viral replicative cycle or according to their clinical use (see Table 47–1).

Common Antiviral Agents ***Influenza.*** **Amantadine and rimantadine** are primarily used against infections caused by **influenza A.** Their mechanism of action is interfering with **viral uncoating.** Anti-influenza agents decrease the duration of illness by 1 to 2 days and decrease the intensity of the illness by 50 percent. They must be started within the first 48 to 72 hours on onset to be effective. Both agents are fairly well absorbed orally and cause some minor central nervous system (CNS) effects (rimantadine less so) and minor GI effects.

Herpes Virus, Varicella-Zoster Virus/Cytomegalovirus **Acyclovir** is used against **herpes simplex virus 1 and herpes simplex virus 2.** Acyclovir, a **nucleoside DNA polymerase inhibitor,** is a deoxyguanosine triphosphate **(dGTP) analog** that is incorporated into the viral DNA and causes DNA chain termination. Its specificity is a result of the presence of **herpes-specific thymidine kinase** in infected cells, which phosphorylates acyclovir; this does not occur in uninfected cells. The acyclovir triphosphate is formed in infected cells and incorporated into infected

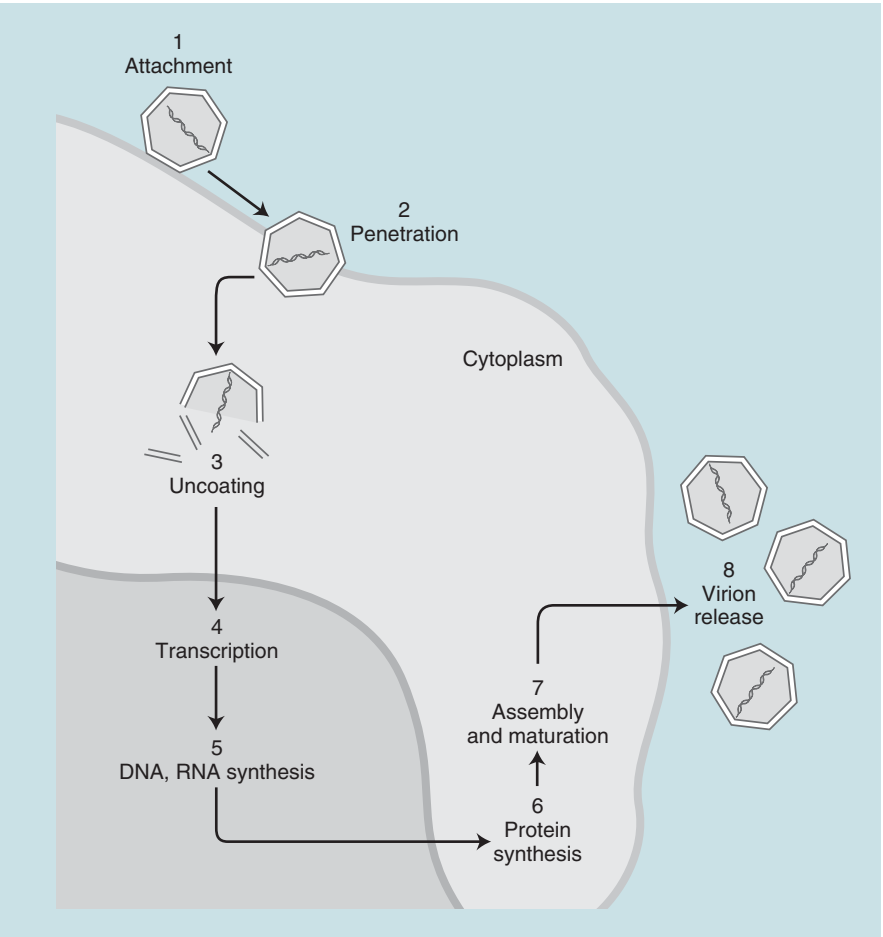

Figure 47–1.

cells' DNA, and not formed in normal cells. Acyclovir can be used topically, orally for recurrent genital herpes, and IV for immunocompromised patients or herpes encephalitis. Its adverse effects include headache, nausea, and rarely nephrotoxicity with IV use. **Valacyclovir** is an analog of acyclovir and is converted to acyclovir in the body. Its advantage is better bioavailability.

Penciclovir is converted to the triphosphate form and inhibits viral DNA polymerase. **Famciclovir** is converted to the active agent penciclovir in the body. Their main use is to treat **localized herpes zoster in immunocompromised patients.** Headache and GI effects are common. **Ganciclovir** is structurally similar to acyclovir and must be converted to the triphosphate form to be active; it competes with dGTP for incorporation into viral DNA, thereby inhibiting DNA polymerase. Its primary role is against **cytomegalovirus,** and is **far more effective than acyclovir against cytomegalovirus.** Ganciclovir can induce serious **myelosuppression.**

Table 47–1 • EXAMPLES OF ANTIVIRAL MECHANISMS

	Viral Life Cycle	Antiviral Therapy	Examples
1.	Virus attaches to the cell	γ-globulin (binds to virus)	Hepatitis A and B
2.	Virus penetrates the cell	γ-globulin	
3.	Virus uncoats its nucleic acid	Amentadine, rimantodine	Influenza A
4a.	Synthesis of key viral enzymes such as polymerases (transcription)	Acyclovir, ribavirin (DNA polymerase inhibitor)	Herpes simplex
4b.	Viral nucleic acid is synthesized	Zidovudine (reverse transcriptase inhibitor)	HIV
5.	Late viral structural proteins are synthesized	Indinavir (protease inhibitor)	HIV
6.	Viral proteins and particles are assembled	Interferons	Hepatitis C virus
7.	Viruses are released from the host cell	Zanmivir, oseltamivir	Influenza A and B

Foscarnet is a **synthetic nonnucleoside analog of pyrophosphate** and inhibits DNA polymerase or HIV reverse transcriptase by directly binding to the pyrophosphate-binding site. Its use is usually for **acyclovir-resistant herpes or cytomegalovirus retinitis.** Significant nephrotoxicity may occur with its use.

Trifluridine is a **fluorinated pyrimidine nucleoside analog.** Its monophosphate form inhibits thymidylate synthetase, and its triphosphate form inhibits DNA polymerase. It is active against herpes simplex virus 1 and 2 and cytomegalovirus, and it is used primarily against keratoconjunctivitis and recurrent keratitis.

HIV HIV is typically treated using three antiretroviral drugs simultaneously, from at least two of the five classes, which include **nucleoside/nucleotide reverse transcriptase inhibitors** (zidovudine also called AZT, abacavir, lamivudine, stavudine, didanosine)**, nonnucleoside reverse transcriptase inhibitors** (nevirapine, efavirenz, delavirdine), **protease inhibitors** (indinavir, nelfinavir, saquinavir), **fusion inhibitors** (enfuvirtide), **integrase inhibitors** (raltegravir), and **CCR5 antagonists** (maraviroc).

Hepatitis C Virus Hepatitis C virus is treated with **interferon and ribavirin**. Interferon is typically administered in the form of peginterferon; pegylation increases the half-life and decreases immunogenicity. Interferon is a nonnucleoside transcription inhibitor. **Ribavirin** inhibits RNA polymerase activity, thereby inhibiting the initiation and synthesis of RNA fragments. Patients with hepatitis C genotype 1 may also benefit from the addition of a protease inhibitor (telaprevir or bocepravir), which are inhibitors of the nonstructural protein 3 (NS3) complex to inhibit replication of the hepatitis C virus. Telapravir can inhibit this complex in other hepatitis C genotypes, but bocepravir specifically acts on hepatitis C genotype 1. Protease inhibitors are not recommended for genotypes 2, 3. and 4.

Table 47–2 • PARTIAL LISTING OF ANTIVIRAL AGENTS AND MECHANISMS OF ACTION

Nucleosides that inhibit RNA or DNA genomic replication: acyclovir, cidofovir, famciclovir, ganciclovir/valganciclovir, penciclovir, idoxuridine, trifluridine, valacyclovir
Nonnucleosides that inhibit RNA or DNA genomic replication: foscarnet
Nonnucleosides that inhibit transcription: interferons
Nonnucleosides that inhibit translation: fomivirsen
Nonnucleosides that inhibit uncoating: amantadine, rimantadine
Nonnucleosides that inhibit release and budding: zanamivir, oseltamivir
Other Viral Infections
Hepatitis B and C: Lamivudine, adefovir, interferon alfa, and ribavirin
Influenza: Amantadine and rimantadine (nonnucleosides that inhibit uncoating), zanamivir and oseltamivir (nonnucleosides that inhibit release and budding)
HIV-1: Nucleoside and nucleotide reverse transcriptase inhibitors (NRTIs; abacavir, didanosine, lamivudine, stavudine, tenofovir, zalcitabine, zidovudine)
Nonnucleoside reverse transcriptase inhibitors (NNRTIs; delavirdine, efavirenz, nevirapine)
Protease inhibitors (amprenavir, atazanavir, fosamprenavir, indinavir, lopinavir/ritinovir, nelfinavir, ritonavir, saquinavir, tipranavir)
Fusion inhibitors (enfuvirtide)

Interferon is associated with significant adverse effects, including fatigue, arthralgias, depression, and suicidality.

Structure

Valacyclovir, famciclovir, and valganciclovir: Ester prodrugs of, respectively, acyclovir, penciclovir, and ganciclovir.

Cidofovir: Phosphonate analog of cytidine.

Idoxuridine, stavudine, zidovudine: Analog of thymidine.

Lamivudine: Analog of cytosine.

Abacavir: Analog of guanosine.

Didanosine: analog of adenosine

Table 47–2 presents a partial listing of antiviral agents and mechanisms of action, and Table 47–3 presents the agents used to treat herpes simplex virus, varicella-zoster virus, and cytomegalovirus.

Mechanism of Action

Valacyclovir, ganciclovir, and valganciclovir act like acyclovir.

Idoxuridine and famciclovir and the prodrug famciclovir, which is converted to the active agent penciclovir, also act like acyclovir except that they do not cause DNA chain termination.

Trifluridine (activated by host cell phosphorylation) and foscarnet (acts directly to inhibit viral DNA polymerase and RNA polymerase) do not require activation by

Table 47–3 • AGENTS USED TO TREAT HERPES SIMPLEX VIRUS, VARICELLA-ZOSTER VIRUS, AND CYTOMEGALOVIRUS (ROUTE OF ADMINISTRATION)

Agents	Viral Infections	Adverse Effects
Acyclovir (t,o,p)	Herpes simplex virus, varicella-zoster virus	Nausea, vomiting, diarrhea, headache; parenteral administration may cause reversible neuropathy and nephropathy
Cidofovir (p)	Herpes simplex virus, cytomegalovirus	Nephrotoxicity
Docosanol (t)	Herpes simplex virus, varicella-zoster virus	Well tolerated
Famciclovir (o)	Herpes simplex virus, varicella-zoster virus	Nausea, vomiting, diarrhea, headache, confusion in elderly
Ganciclovir (intraocular implant, o,p)	Cytomegalovirus	Generally reversible myelosuppression with neutropenia and thrombocytopenia
Valganciclovir (o)		
Penciclovir (t)	Herpes simplex virus, varicella-zoster virus	Well tolerated
Idoxuridine (o)	Herpes simplex virus	Edema and burning and stinging of the eye
Valacyclovir (o)	Herpes simplex virus,	Nausea, vomiting, diarrhea, headache
Trifluridine (t)	Herpes simplex virus, varicella-zoster virus	Edema and burning and stinging of the eye
Foscarnet (p)	Herpes simplex virus, varicella-zoster virus, cytomegalovirus	Reversible nephrotoxicity, hypo- or hypercalcemia and phosphatemia that may lead to neural and cardiac dysfunction; hallucinations, genital ulceration, and anemia are not uncommon
Fomivirsen (p)	Cytomegalovirus	Iritis, vitreitis, increased ocular pressure

t = topical, o = oral, p = parenteral.

viral thymidine kinase for their activity and therefore can be used to treat acyclovir-resistant viral infections.

Cidofovir is phosphorylated to mono- and diphosphate nucleotides by cellular kinases and, therefore, accumulates in both infected and uninfected cells. As a diphosphate, cidofovir inhibits and serves as an alternative dCTP substrate for viral DNA polymerase, resulting in inhibition of viral DNA synthesis and termination of chain elongation.

Fomivirsen is an antisense oligonucleotide that binds to the major immediate early region 2 (IE_2) of cytomegalovirus mRNA to prevent its translation to protein and therefore to block viral replication.

Neverapine, efavirenz, and delavirdine bind to reverse trancriptase to inhibit its activity.

Administration

Acyclovir: Administered IV and orally and is used as a topical agent.

Foscarnet: Reserved to treat acyclovir-resistant viral infections and can only be administered IV.

Valacyclovir, famciclovir: Available only for oral use.

Ganciclovir: Administered orally; parenterally (IV); and as an intraocular, slow-release implant.

Penciclovir, trifluridine, idoxuridine: Available only for topical use.

Cidofovir: Administered parenterally with probenecid to block its active tubular secretion.

Fomivirsen: Administered by intravitreal injection.

Pharmacokinetics

Acyclovir: Low oral bioavailability.

Vlacyclovir: An ester prodrug with greater oral bioavailability than acyclovir that is rapidly and completely converted to acyclovir after absorption.

Famciclovir, valganciclovir: Ester prodrugs that are rapidly converted by first-pass metabolism to their respective active agents, penciclovir and ganciclovir.

NNRTI and PI agents are metabolized by and induce the cypP450 enzyme system (3A4), resulting in numerous drug-drug interactions.

COMPREHENSION QUESTIONS

47.1 Which of the following drugs is most likely to cause myelosuppression?

A. Famciclovir
B. Fomivirsen
C. Ganciclovir
D. Penciclovir

47.2 Which of the following drugs is a prodrug that after oral administration is converted to an active agent, penciclovir?

A. Acyclovir
B. Famciclovir
C. Fomivirsen
D. Ganciclovir

47.3 The high levels of acyclovir obtained in target viruses such as herpes simplex virus is a result of which of its properties?

A. Binding to the major immediate early region 2 (IE_2) of cytomegalovirus mRNA
B. Direct inhibition of viral DNA polymerase and RNA polymerase
C. Host cell enzyme conversion to triphosphate compounds
D. Monophosphorylation by viral thymidine kinase

ANSWERS

47.1 **C.** Ganciclovir can cause a generally reversible myelosuppression. Famciclovir can cause nausea, vomiting, diarrhea, and headache. Penciclovir is generally well tolerated. Fomivirsen causes ocular problems, including iritis, vitreitis, and increased ocular pressure.

47.2 **B.** Famciclovir is a diacetyl ester prodrug that after oral administration is converted to penciclovir by first-pass metabolism. Fomivirsen is administered by intravitreal injection. Acyclovir and ganciclovir act directly and can be administered orally and parenterally. Acyclovir can also be administered topically. Ganciclovir can also be administered as an intraocular implant.

47.3 **D.** The high levels of acyclovir obtained in target viruses such as herpes simplex virus result from its monophosphorylation by viral thymidine kinase. Antiviral drugs that are activated only by host cell kinases, for example, cidofovir, will accumulate in host cells with or without viral infection. Fomivirsen is an antisense oligonucleotide that binds to the major immediate early region 2 (IE_2) of cytomegalovirus mRNA to prevent its translation to protein and therefore to block viral replication. Foscarnet acts directly to inhibit viral DNA polymerase and RNA polymerase.

PHARMACOLOGY PEARLS

- The primary strategy of antiviral agents is to attack a unique but vital viral enzyme or process.
- The three major types of antiviral agents include DNA polymerase inhibitors, reverse transcriptase inhibitors, and protease inhibitors.
- HIV therapy generally uses at least two reverse transcriptase inhibitors and one protease inhibitor.
- Didanosine is also a nucleoside reverse transcriptase inhibitor for HIV infections and is associated with peripheral neuropathy and pancreatic damage.
- Foscarnet is a synthetic nonnucleoside analog of pyrophosphate and is associated with reversible nephrotoxicity, and hypo- or hypercalcemia and phosphatemia that may lead to neural and cardiac dysfunction. Also, hallucinations, genital ulceration, and anemia may occur.
- Implantable ganciclovir and oral valganciclovir are more widely used for cytomegalovirus disease than the iv agents foscarnet, cidofovir, and ganciclovir.

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AIDS info: U.S. Department of Health and Human Services. www.aidsinfo.nih.gov

CASE 48

A 4-year-old boy is brought in by his mother because he keeps scratching a spot on his arm. His mother says that this has been going on for several days, and it appears that the spot is growing larger. No one else at home has anything similar. He has not had a fever or any systemic signs of illness. There have been no recent exposures to new foods, medications, lotions, or soaps. He attends preschool during the day. On examination of his skin you see a circular, nickel-sized ring on his right forearm. It has a red, raised border with active scale at the borders only, and central clearing. You obtain a potassium hydroxide scraping of the lesion and is found to be positive with fungal elements. The remainder of his skin examination and his general physical examination are normal. You diagnose him with tinea corporis (ringworm) and prescribe topical nystatin.

- What is the mechanism of action of nystatin?
- Nystatin is similar in structure and function to which other antifungal medication?

ANSWERS TO CASE 48:
Antifungal

Summary: A 4-year-old boy with tinea corporis is prescribed topical nystatin.

- **Mechanism of action of nystatin:** Creates pores in fungal membranes by binding ergosterol.
- **Nystatin is similar in structure and action to:** Amphotericin B.

CLINICAL CORRELATION

Superficial fungal infections of the skin are very common, particularly in the pediatric population. There are many topical preparations available that are effective against this problem. Nystatin is a polyene antifungal agent with similarities in structure and function to the systemic antifungal agent amphotericin B. Nystatin, which is too toxic for parenteral use, is administered topically for skin infections. It is not absorbed through the GI tract; therefore, oral preparations are used only to treat fungal infections of the mucous membranes of the mouth or intestinal tract. Amphotericin B is given IV and is only used for severe, systemic fungal infections. It has significant toxicities and adverse effects. It frequently causes fever, chills, and impaired renal function. Less often it will cause anaphylactic reactions, pain, thrombocytopenia, and seizures.

APPROACH TO:
Pharmacology of Antifungal Drugs

OBJECTIVES

1. List the antifungal drugs and describe their mechanisms of action, therapeutic uses, routes of administration, and adverse effects.

DISCUSSION

Class

In addition to the pyrimidine analog, flucytosine, and the *Penicillium*-derived antifungal agent, griseofulvin, the four major classes of antifungal agents are the polyene macrolides, azoles, allylamines, and echinocandins (Table 48–1).

Of all the available antifungal agents, **amphotericin B** has the broadest spectrum of activity, including activity against **yeast, mycoses, and molds.** Although this drug was long considered the first-line drug of choice, its use is now limited due to serious adverse effects. The **major adverse effect** resulting from amphotericin B administration is the almost invariable **renal toxicity** that results from decreased renal blood flow and from tubular and basement membrane destruction that may be irreversible

Table 48–1 • SELECTED ANTIFUNGAL DRUGS (ROUTE)

Polyene Macrolides Nystatin (t,o for GI tract) Natamycin (t) Amphotericin B (t,o for GI tract, p)	*Allylamines* Naftifine (t) Terbinafine (o,t)
Azoles Miconazole (t) Clotrimazole (t) Itraconazole (o,p) Fluconazole (o,p) Voriconazole (o,p)	*Other Antifungal Agents* Flucytosine (o) Griseofulvin (o)
Echinocandins Caspofungin (p) Anidulafungin (p) Micafungin (p)	

t = topical, o = oral, p = parenteral.

and may require dialysis. Therefore, it is often given acutely to patients with severe infections followed soon after by a less toxic agent such as an azole. Other adverse effects of amphotericin B relate to its IV infusion and include fever, chills, vomiting, hypotension, and headache, which can be ameliorated somewhat by careful monitoring and slow infusion.

The **azole antifungal agents** have a **broad spectrum of activity,** including activity against **vaginitis, candidiasis, mycoses, and dermatophytes,** among many others. As topical agents the azoles are relatively safe. When administered orally, their **most common adverse effect is GI dysfunction. Fluconazole, itraconazole, and voriconazole** can also be administered parenterally. Hepatic dysfunction may rarely occur. **Itraconazole** interaction with quinidine can result in cardiac arrhythmias. Monitoring patients who receive itraconazole for potential **hepatic toxicity** is also highly recommended. **Voriconazole** frequently causes an **acute blurring of vision** with changes in color perception that resolves quickly.

The **allylamine antifungal agents, naftifine and terbinafine,** are used **topically** to treat dermatophytes. Contact with mucous membranes may lead to local irritation and erythema and should be avoided. **Terbinafine** administered orally is effective against the **onychomycosis. Monitoring for potential hepatic toxicity is highly recommended.**

Flucytosine is active against only a **relatively restricted range of fungal infections.** Because of rapid development of resistance, it is used concomitantly for its synergistic effects with other antifungal agents. The most commonly reported adverse effect is **bone marrow suppression,** probably as a result of the **toxicity of the metabolite fluorouracil,** which should be continuously monitored. Other reported but less common adverse effects include reversible hepatotoxicity, enterocolitis, and hair loss.

Griseofulvin, the use of which is declining relative to the azoles terbinafine and itraconazole, is an effective antifungal agent that is used only **systemically** to treat a very **limited range of dermatophyte infections.** The most common adverse effects include **hypersensitivity** (fever, skin rash, serum sickness-like syndrome) and **headache.** It is **teratogenic.**

The **echinocandins** are highly effective against **many species of candida**. They are the first antifungals to target the fungal cell wall. They have become the **first-line drug of choice for candidemia** and are available for parenteral administration. Side effects include fever, mild hepatotoxicity, infusion hypersensitivity reactions, and GI symptoms. Rarely, they cause bone marrow suppression. Unlike amphoterin B, they do not affect renal function. Currently, there is minimal resistance to echinocandins, whereas resistance to azoles is on the rise.

Structure

Depending on whether there are two or three nitrogen atoms in the azole ring, azole antifungal agents are subclassified, respectively, as either imidazoles (ketoconazole, clotrimazole, miconazole) or triazoles (itraconazole, fluconazole, voriconazole). Echinocandins are cyclic hexapeptides.

Mechanism of Action

Nystatin and amphotericin B bind to ergosterol, a major component of **fungal cell membranes.** This disrupts the stability of the cell by forming pores in the cell membrane that result in leakage of intracellular constituents. Bacteria are not susceptible to this because they lack ergosterol.

Azoles (imidazoles less so) have a greater affinity for fungal than human cytochrome P450 enzymes and, therefore, more effectively reduce the synthesis of fungal cell ergosterol than human cell cholesterol. The allylamine antifungal agents, naftifine and terbinafine, decrease ergosterol synthesis and increase fungal membrane disruption by inhibiting the enzyme squalene epoxidase.

Flucytosine must first be transported into fungal cells via a cytosine permease and converted to 5-fluorouracil (5-FU) and then sequentially converted to 5-fluorodeoxyuridylic acid, which disrupts DNA synthesis by inhibiting thymidylate synthetase. Human cells are unable to synthesize the active flucytosine metabolites.

The mechanism of antifungal action of griseofulvin is not clearly known. It acts only on growing skin cells and has been reported to interfere with nucleic acid synthesis and disrupt microtubule function, among other activities.

Echinocandins are the first antifungals to specifically target the fungal cell wall. They inhibit the β–1,3-glucan synthase, an enzyme required for the synthesis of an important cell-wall component, glucan, rendering cell walls more susceptible to lysis. β-glucans are not present in human cells, thereby reducing the potential for toxicity in humans.

Administration

Amphotericin B is insoluble in water and, therefore, is generally administered as a colloidal suspension with sodium deoxycholate. Because of its poor absorption from the GI tract, amphotericin B must be given IV to treat systemic disease, although it is effective orally for fungal infections within the GI lumen. Likewise, nystatin is poorly absorbed but may also be used for fungal infection of the GI tract. It is too toxic for systemic use and, therefore, is mostly used topically to treat fungal infections of the skin and mucous membranes (eg, oropharyngeal thrush, vaginal candidiasis). Costly lipid formulations of amphotericin B are available for IV use,

which reduce its nonspecific binding to cholesterol of human cell membranes and therefore lessens its potential to cause renal damage. Griseofulvin is administered in a microparticulate form to improve absorption.

Echinocandins are administered parenterally. Azoles are available in oral and parenteral preparations.

Pharmacokinetics

Amphotericin B and nystatin are poorly absorbed from the GI tract. The absorption of the azole antifungal agent, itraconazole, is reduced by antacids that block acid secretion. Through their actions on hepatic microsomal enzymes, itraconazole and voriconazole significantly decrease the metabolism of numerous other drugs (eg, the rifamycins, phenytoin, carbamazepine, digoxin, cyclosporine). In the presence of a number of these other drugs, the metabolism of itraconazole and voriconazole may be increased.

Echinocandins are large-molecular-weight compounds that are poorly absorbed by the GI tract. In the circulation, they are highly bound to proteins and do not cross the blood-brain barrier. Caspofungin can affect hepatic cytochrome P450 enzymes and has significant potential drug-drug interactions. Micafungin is metabolized by arylsulfatase, catechol-*O*-methyltransferase, and hydroxylation, and has few drug-drug interactions. Anidulafungin is not metabolized and excreted via the fecal route.

COMPREHENSION QUESTIONS

48.1 Which of the following antifungal agents binds to ergosterol?

A. Amphotericin B
B. Fluconazole
C. Flucytosine
D. Terbinafine

48.2 A 45-year-old man is placed on an antifungal agent for systemic infection. He is noted to have decreased serum leukocyte and platelet counts. Bone marrow suppression is a common adverse effect of which of the following drugs?

A. Fluconazole
B. Flucytosine
C. Griseofulvin
D. Terbinafine

48.3 Which class of antifungals inhibits the synthesis of the fungal cell wall?

A. Polyene macrolides
B. Allylamines
C. Azoles
D. Echinocandins

ANSWERS

48.1 **A.** Amphotericin B, like nystatin, binds to ergosterol to create pores in fungal membranes. Flucytosine must first be transported into fungal cells via a cytosine permease and converted to 5-FU and then sequentially converted to 5-fluorodeoxyuridylic acid, which disrupts DNA synthesis by inhibiting thymidylate synthetase. Fluconazole binds fungal cell cytochrome P450 enzymes to reduce the synthesis of ergosterol. Terbinafine decreases ergosterol synthesis by inhibiting the enzyme squalene epoxidase.

48.2 **B.** Bone marrow suppression is a common adverse effect of flucytosine. A common adverse effect of griseofulvin is hypersensitivity (fever, skin rash, serum sickness-like syndrome). Terbinafine may cause hepatic toxicity. Fluconazole causes GI dysfunction.

48.3 **D.** Echinocandins are the first class of drug to affect synthesis of the fungal cell wall. They inhibit the β–1,3-glucan synthase, an enzyme required for the synthesis of an important cell-wall component, glucan, rendering cell walls more susceptible to lysis. Azoles reduce the synthesis of fungal cell ergosterol. Polyene macrolides bind to ergosterol, a major component of fungal cell membranes. This disrupts the stability of the cell by forming pores in the cell membrane that result in leakage of intracellular constituents. The allylamine antifungal agents decrease ergosterol synthesis and increase fungal membrane disruption by inhibiting the enzyme squalene epoxidase.

PHARMACOLOGY PEARLS

- Itraconazole has been associated with heart failure when used to treat onychomycosis and, therefore, should not be used in patients with ventricular abnormalities.
- A common side effect of griseofulvin is hypersensitivity.
- Echinocandins are the first-line drug of choice for a variety of systemic fungal infections.

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CASE 49

A 66-year-old man presents for evaluation of skin growths on his face. For several years he has had scaly, rough growths on his face, forehead, and scalp. He has had individual lesions removed by previous physicians, but keeps getting more and more. He has never been diagnosed with skin cancer. He has a long history of sun exposure and multiple sunburns, primarily as a consequence of working outdoors and playing golf. He takes an aspirin a day and pravastatin for high cholesterol. He has no other significant medical history. On examination of his skin, you note multiple 4- to 7-mm lesions on the face and scalp that are flat, pink, and scaly. They feel rough on palpation. They are all in areas that would be exposed to the sun. He has several on the dorsal surfaces of his hands and forearms. You diagnose him as having multiple actinic keratoses. Along with recommending skin protection from the sun, you prescribe topical 5-fluorouracil (5-FU).

- What is the mechanism of action of 5-FU?
- What are the adverse effects of 5-FU when given systemically?

ANSWERS TO CASE 49:
Alkylating and Antimetabolite Agents

Summary: A 66-year-old man with multiple actinic keratoses is prescribed 5-FU.

- **Mechanism of action of 5-FU:** Pyrimidine antagonist that, after a complex conversion to 5-fluoro-2'-deoxyuridine-5'-monophosphate (FdUMP), covalently inhibits thymidylate synthetase and thus impairs DNA synthesis, thereby preventing cell proliferation and inducing cell death.
- **Adverse effects of systemic 5-FU:** Myelosuppression, nausea, vomiting, and hair loss.

CLINICAL CORRELATION

Actinic keratoses are premalignant skin lesions that frequently occur as a result of excessive sun exposure. Untreated, actinic keratoses may progress to become squamous cell carcinomas of the skin. Persons with multiple lesions are often treated with topical 5-FU. Other pharmacologic treatments for actinic keratosis include topical imiquod cream and ingenol mebutate gel. Systemic 5-FU is given parenterally primarily for the treatment of certain solid tumors. Systemic 5-FU is myelosuppressive and causes frequent GI disturbances and hair loss. Topical 5-FU does not have the systemic side effects but can cause significant local redness, itching, and burning of the skin.

APPROACH TO:
Pharmacology of Alkylating and Antimetabolite Agents

OBJECTIVES

1. Outline the principles of cancer chemotherapy and the development of resistance to chemotherapeutic agents.
2. List the antimetabolite and alkylating chemotherapeutic agents and describe their mechanisms of action, therapeutic uses, and adverse effects.

DISCUSSION

Class

Appropriate **cancer chemotherapy** demands a thorough understanding of the kinetics of **tumor cell growth,** including its **control and regulation,** a thorough understanding of the **pharmacologic properties of available anticancer agents,** and an appreciation of the interactions between them.

Combination chemotherapy early in therapy increases the likelihood of destroying drug-resistant populations of cells that are refractory to treatment and therefore

is **generally more effective than monotherapy.** To be most effective, the drugs used in combination chemotherapy should each have **therapeutic activity with different dose-limiting toxicities** and should be **administered during several cycles** of treatment **to allow recovery from acute adverse effects.**

The drugs used to treat cancer are **classified** as **alkylating agents, antimetabolites, cytotoxic antibiotics, plant alkaloids, hormonal agents, and miscellaneous agents**. This case focuses primarily on the alkylating agents and antimetabolites (Table 49–1). Depending on the tumor type, they are often used in combinations or as adjunct therapy to surgical and radiation procedures.

Primary resistance to anticancer drugs is thought to occur because of some **inherent genetic characteristics of tumor cells. Acquired resistance** of tumor cells to a specific anticancer drug may occur via several different mechanisms that usually involve either **amplification or overexpression of one or more genes.** For example, resistance to methotrexate is caused by either decreased drug transport into tumor cells, a modification of the target enzyme dihydrofolate reductase (DHFR) that results in a decreased affinity for methotrexate, or an increased level of DHFR in tumor cells. Resistance to the chemotherapeutic effects of alkylating agents may develop because of decreased cell permeability, increased cell thiol content that serves as a "decoy" target for alkylation, increased activity of glutathione transferases, and modification of DNA repair mechanisms. Alternatively, after exposure of a tumor cell to a number of structurally different agents, a so-called multidrug, or pleiotropic, resistance may develop to chemotherapeutic agents because of decreased uptake or retention of the drugs. This is a result of either increased expression of the constitutively expressed multidrug resistance gene (MDR-1), which codes for a surface cell membrane P-glycoprotein involved in drug efflux, or by overproduction of one of a number of other multidrug resistance proteins, for example, MRP-1, that are involved in the transmembrane export of drugs. Multidrug resistance is the major form of resistance to vinca alkaloids, etoposide, paclitaxel, anthracyclines, and dactinomycin.

Other Classes of Selected Anticancer Drugs **Cytotoxic antibiotics:** Dactinomycin (actinomycin D), bleomycin, doxorubicin.

Plant alkaloids: Vinblastine, vincristine, vinorelbine, etoposide, paclitaxel, topotecan.

Hormonal agents: Steroid hormones: megestrol acetate, hydrocortisone, prednisone.

Antiandrogens: Flutamide.

Antiestrogens: Tamoxifen.

Gonadotropic-releasing hormone (GRH) agonists: Goserelin acetate, leuprolide.

Aromatase inhibitors: Aminoglutethimide, anastrozole, exemestane, letrozole.

Growth factor receptor inhibitors: Cetuximab, gefitinib, erlotinib, bevacizumab.

Miscellaneous agents: Cisplatin, imatinib, hydroxyurea, mitotane, arsenic trioxide, procarbazine.

Mechanism of Action

Alkylating Agents The cytotoxic effects of alkylating agents result from the transfer of their alkyl groups to numerous cellular components, most notably the bases of

TABLE 49–1 • ANTICANCER DRUGS: ALKYLATING AGENTS AND ANTIMETABOLITES (MAY BE COMBINED WITH OTHER ANTICANCER AGENTS)

Drug Class	Type	Selected Agents	Selected Indications	Toxicity—Acute and Delayed
Alkylating agents	Nitrogen mustards	Cyclophosphamide Ifosfamide Methchlorethamine Mephalan Chlorambucil	Acute and chronic lymphocytic leukemia, non-Hodgkin lymphomas, Hodgkin disease, multiple myeloma; breast, ovary, lung cancer Hodgkin disease Multiple myeloma Chronic lymphatic leukemia	*Alkylating agents:* Nausea and vomiting, GI, ulceration, alopecia, myelosuppression, bone marrow depression (thrombocytopenia, leucopenia), with bleeding
	Methylhydrazine derivatives	Procarbazine	Hodgkin disease	Leukopenia, thrombocytopenia, GI disturbances
	Alkyl sulfonate	Busulfan	Chronic myelogenous leukemia	Thrombocytopenia, GI disturbances
	Nitrosoureas	Carmustine Bendamustine	Hodgkin disease, non-Hodgkin lymphoma, glioblastoma Non-Hodgkin lymphoma	Leukopenia, nausea, vomiting, myelosuppression Leukopenia, nausea, vomiting, myelosuppression
	Triazines	Dacarbazine Temozolamide	Melanoma, Hodgkin disease, soft tissue sarcoma Malignant gliomas	Nausea and vomiting Nausea and vomiting
	Platinum complexes	Cisplatin, carboplatin, oxyplatin	Testicular, ovarian, bladder esophageal, lung, head and neck, colon cancers	Nephrotoxicity, ototoxicity, peripheral neuropathy

Antimetabolites	Folic acid analogs	Methotrexate	Acute lymphcytic leukemia, osteogenic sarcoma, bladder cancer	Diarrhea, mucositis, myelosuppression
		Pemetrexed	Mesothelioma, lung cancer	Diarrhea, mucositis, myelosuppression
	Pyrimidine analogs	Fluorouracil Cytarabine Gemcitabine 5-aza-cytidine	Breast, colon, esophageal, head and neck, stomach cancers, premalignant skin lesions Acute lymphocytic and myelogenous leukemia Pancreatic, ovarian, lung cancer Myelodysplasia	Nausea, vomiting, diarrhea, myelosuppression, neurotoxicity, head and foot syndrome Myelosuppression, GI disturbances, hepatic enzyme elevation, noncardiogenic pulmonary edema Myelosuppression Myelosuppression
	Purine analogs	Mercaptopurine Pentostatin Fludarabine Clofarabine Nelarabine	Acute lymphocytic and myelogenous leukemia Hairy cell leukemia, chronic lymphocytic leukemia Chronic lymphocytic leukemia Acute myelogenous leukemia T-cell leukemia, lymphoma	Bone marrow depression, anorexia, nausea, vomiting Myelosuppression, abnormal liver function, skin rash Myelosuppression, nausea, vomiting Myelosuppression, hypotension, pulmonary edema Myelosuppression, seizures, delirium, somnolence

DNA, particularly the N7 position of guanine, which in replicating cells (G_1 and S phase) results in either miscoding or strand breakage.

Antimetabolites **Methotrexate (MTX):** Folic acid antagonist that binds the catalytic site of DHFR to reduce the synthesis of tetrahydrofolate that results in downstream reduction of thymidylate and an indirect inhibition of DNA synthesis as well as RNA and protein synthesis.

Fluorouracil (5-FU): A prodrug that is converted to FdUMP by a multistep process. FdUMP covalently forms an inhibitory ternary complex with the enzyme thymidylate synthetase and reduced folate *N*5,10-methylene tetrahydrofolate, which are essential to the synthesis of thymidylate and the production of DNA. Through other metabolic conversions, 5-FU is also incorporated into DNA as 5-fluorodeoxyuridine-5-triphosphate (FdUTP) and into RNA as 5-fluorouridine-5-triphosphate (FUTP), which results in further inhibition of DNA function as well as inhibition of RNA processing and mRNA activity.

Mercaptopurine (6-MP): The precise mechanism of action of mercaptopurine, a modified purine, is unknown. Like the natural purines, hypoxanthine and guanine, it is converted to a nucleotide by hypoxanthine guanine phosphoribosyltransferase (HGPRT). The product, in this case 6-thioinosinic acid, inhibits purine nucleotide interconversion.

Pharmacokinetics

Cyclophosphamide is not itself cytotoxic but must first be converted by hepatic microsomal enzymes to form the cytotoxic agents, phosphoramide mustard and acrolein.

COMPREHENSION QUESTIONS

49.1 Resistance to methotrexate is a result of which of the following?

A. Increased activity of glutathione transferases
B. Increased cell thiol content
C. Modification of DNA repair mechanisms
D. Modification of the target enzyme DHFR

49.2 Which of the following agent forms an inhibitory ternary complex with the enzyme thymidylate synthetase?

A. Cyclophosphamide
B. Fluorouracil (5-FU)
C. Mercaptopurine (6-MP)
D. Methotrexate (MTX)

49.3 Which of the following is true in general of combination cancer chemotherapy?

A. It is administered during several cycles of treatment.

B. It is less effective than monotherapy.

C. It includes at least two drugs with similar dose-limiting toxicities.

D. It includes one drug that has no inherent therapeutic activity.

ANSWERS

49.1 **D.** Resistance to methotrexate may be a result of a modification of the target enzyme DHFR. It may also be a consequence of decreased drug transport into tumor cells or an increased level of DHFR in tumor cells. Resistance to the chemotherapeutic effects of alkylating agents may develop because of decreased cell permeability; increased cell thiol content, which serves as a "decoy" target for alkylation; increased activity of glutathione transferases; and modification of DNA repair mechanisms.

49.2 **B.** Fluorouracil (5-FU) is a prodrug that is converted to FdUMP, which covalently forms an inhibitory ternary complex with the enzyme thymidylate synthetase and reduced folate *N*5,10-methylene tetrahydrofolate, both of which are essential to the synthesis of thymidylate and the production of DNA. Mercaptopurine (6-MP) is thought to inhibit purine nucleotide interconversion. Methotrexate (MTX) is a folic acid antagonist that binds the catalytic site of DHFR to reduce the synthesis of tetrahydrofolate that results in downstream reduction of thymidylate and an indirect inhibition of DNA synthesis as well as RNA and protein synthesis. The cytotoxic effects of alkylating agents like cyclophosphamide are a result of the transfer of their alkyl groups to numerous cellular components, most notably the bases of DNA that in replicating cells (G_1 and S phase) results in either miscoding or strand breakage.

49.3 **A.** Combination chemotherapy early in therapy increases the likelihood of destroying drug-resistant populations of cells that are refractory to treatment and therefore is generally more effective than monotherapy. To be most effective, the drugs used in combination chemotherapy should each have therapeutic activity with different dose-limiting toxicities and should be administered during several cycles of treatment to allow recovery from acute adverse effect.

PHARMACOLOGY PEARLS

- Smaller tumors are generally more responsive to chemotherapy than larger tumors because of the increased probability of drug-resistant mutations in the larger tumors.
- Development of a mild leukopenia is evidence of the adequate absorption of orally administered alkylating agents.
- Leucovorin (citrovorum factor), a folic acid analog that does not require reduction by DHFR, can be used to "rescue" patients from MTX overdose or high-dose MTX therapy.

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CASE 50

A 60-year-old woman presents to her oncologist for follow-up of her metastatic ovarian cancer. She was diagnosed approximately a year ago. Initial treatment included surgery and a cisplatin-based chemotherapy regimen. Unfortunately, she was recently diagnosed with recurrent disease. She currently takes only promethazine as needed for nausea and a combination of hydrocodone and acetaminophen as needed for pain. On examination she appears comfortable. She has a thin growth of hair on her scalp. Her abdomen has a well-healed surgical scar but is otherwise unremarkable. The remainder of her examination is normal. She is diagnosed with recurrent metastatic ovarian cancer and placed on a chemotherapeutic regimen that includes paclitaxel.

- What is the mechanism of action of paclitaxel?
- What are the common adverse reactions seen with paclitaxel?

ANSWERS TO CASE 50:
Plant Anticancer Alkaloids

Summary: A 60-year-old woman with recurrent metastatic ovarian cancer is being treated with combination chemotherapy including paclitaxel.

- **Mechanism of action of paclitaxel:** Promotes formation and inhibits disassembly of stable microtubules, resulting in inhibition of mitosis.
- **Adverse effects of paclitaxel:** Myelosuppression, peripheral neuropathy, GI side effects.

CLINICAL CORRELATION

Paclitaxel is a chemical derived from bark of the Pacific yew tree. Its chemotherapeutic effect is based on its ability to inhibit mitosis. Its mechanism of action is to promote the formation of and inhibit the disassembly of stable microtubules in the M phase of cell division. Paclitaxel is used for the treatment of metastatic ovarian, breast, and small cell lung cancers. It is metabolized in the liver and excreted in the bile. Myelosuppression and peripheral neuropathy are often dose-limiting toxicities, and hypersensitivity reaction, GI side effects, and hair loss are common.

APPROACH TO:
Pharmacology of Plant Anticancer Alkaloids

OBJECTIVES

1. List the plant alkaloids used as cancer chemotherapeutic agents and describe their mechanisms of action, therapeutic uses, and adverse effects.

DEFINITIONS

Microtubules: Structures composed of tubulin polymers that are critical components of the cell cytoskeleton and the mitotic spindle.

Topoisomerases (I and II): Nuclear enzymes that cleave and unwind DNA to relieve torsional stress. They are necessary for DNA replication and RNA transcription. Topoisomerase II is also necessary for mitosis.

DISCUSSION

Class

Table 50–1 describes selected anticancer drugs. See also Case 49.

TABLE 50–1 • SELECTED ANTICANCER DRUGS DERIVED FROM NATURAL PRODUCTS (MAY BE COMBINED WITH OTHER ANTICANCER AGENTS)

Type of Agent	Name	Selected Indications	Selected Toxicities
Vinca alkaloids	Vinblastine Vincristine Vinorelbine	Hodgkin's disease, non-Hodgkin lymphoma, testis cancer Acute lymphocytic leukemia, non-Hodgkin lymphoma, multiple myeloma Non-small cell lung cancer, breast cancer	Nausea and vomiting, myelosuppression, neurotoxicity, alopecia Neurotoxicity (dose limiting) GI dysfunction, myelosuppression, muscular-skeletal disorders, aberrant antidiuretic Myelosuppression (dose limiting), nausea and vomiting, GI dysfunction, neurotoxicity, SIADH
Taxanes	Paclitaxel, docetaxel	Breast cancer and a wide variety of solid tumors	Myelosuppression (dose limiting), nausea and vomiting, hypotension, arrhythmias, neurotoxicity
Epipodophyllotoxins	Etoposide Teniposide	Testicular and ovarian germ cell cancers, lung cancers, acute lymphoblastic leukemia Acute lymphoblastic (children)	Myelosuppression is dose limiting. Nausea and vomiting, mucositis, hypotension Myelosuppression is dose limiting. Nausea and vomiting
Antibiotics Anthracyclines	Actinomycin D Daunorubicin Doxorubicin	Choriocarconoma, Wilms tumor, testis cancer, Kaposi sarcoma Acute myelogenous and acute lymphocytic leukemia Soft tissue and osteogenic sarcoma, genitourinary, thyroid, lung and stomach cancers, neuroblastoma	Anorexia, nausea, vomiting, hematopoietic suppression Cardiomyopathy Cardiomyopathy
Echinocandins	Trabectedin	Soft tissue sarcoma, ovarian cancer	Neutropenia, thrombocytopenia, nausea, vomiting
Anthracenedione	Mitoxantrone Bleomycin Mitomycin C	Breast and prostate cancer Testis and cervical cancer Stomach, anal, lung cancer	Hyperpigmentation, hyperkeratosis
Enzymes	L-Asparaginase	Acute lymphocytic leukemia	anaphylaxis
Camptothecin analogs	Topotecam Irinotecan	Recurrent ovarian, small cell lung cancer Colorectal cancer	Hematological Diarrhea, myelosuppression

Structure

Vinblastine and vincristine are derived from the periwinkle plant (*Vinca rosea*). Vinorelbine is a semisynthetic vinca alkaloid.

Paclitaxel is a complex diterpene derived from the Western and European yew (*Taxus brevifolia* and *Taxus baccata*).

Etoposide is a semisynthetic podophyllotoxin, an extract from the Mandrake root (*Mandragora officinarum*) or May apple root (*Podophyllum peltatum*).

Mechanism of Action

Vinca alkaloids (vinblastine, vincristine, vinorelbine): Bind tubulin to terminate microtubule assembly and cause cell arrest in metaphase (M) by blocking mitosis and chromosomal aggregation and causing mitotic spindle dissolution.

Taxanes (paclitaxel): Bind to microtubules resulting in their stabilization and in an enhancement of aberrant tubulin polymerization that result in cytotoxicity, including mitotic arrest.

Epipodophyllotoxins (etoposide): Reversibly complex with the enzyme topoisomerase II that results in double-stranded DNA strand breakage.

Administration

Hypersensitivity to paclitaxel can be reduced by premedication with dexamethasone and histamine H_1- and H_2-receptor blockers.

Pharmacokinetics

Abraxane is a formulation of paclitaxel bound to albumin, approved for treatment of breast cancer, that does not cause hypersensitivity reactions, and is less likely to result in severe neurotoxicity or myelosuppression.

Vinca alkaloid hepatic metabolism is decreased by L-asparaginase.

Paclitaxel is metabolized extensively by hepatic P450 enzymes (CYP450 3A4) with potential, therefore, of drug-drug interactions. Dose reduction is necessary for patients with liver dysfunction.

Etoposide is 95 percent plasma protein bound. Dose reduction is necessary for patients with renal dysfunction.

COMPREHENSION QUESTIONS

50.1 Which of the following classes of cancer chemotherapeutic agents bind tubulin and cause arrest of cells in metaphase?

A. Alkylating agents
B. Antimetabolites
C. Taxanes
D. Vinca alkaloids

50.2 Abraxane is often used to reduce hypersensitivity to which of the following drugs?

A. Etoposide
B. Paclitaxel
C. Vinblastine
D. Vincristine

50.3 Neurotoxicity is dose-limiting for which of the following drugs?

A. Etoposide
B. Methotrexate
C. Paclitaxel
D. Vincristine

ANSWERS

50.1 **D.** Vinca alkaloids (vinblastine, vincristine, vinorelbine) bind tubulin to terminate microtubule assembly and cause cell arrest in metaphase (M) by blocking mitosis and chromosomal aggregation and causing mitotic spindle dissolution. Alkylating agents form covalent bonds with adjacent guanine residues and inhibit DNA replication and transcription. Antimetabolites compete with naturally occurring compounds for binding sites on enzymes or else become incorporated into DNA or RNA to interfere with cell growth and division. Taxane (paclitaxel) binds to microtubules resulting in their stabilization and in an enhancement of aberrant tubulin polymerization that result in cytotoxicity, including mitotic arrest.

50.2 **B.** Hypersensitivity to paclitaxel can be reduced by abraxane, a formulation of paclitaxel bound to albumin.

50.3 **D.** Neurotoxicity is dose limiting for vincristine. Myelosuppression is dose limiting for paclitaxel, etoposide, and methotrexate.

PHARMACOLOGY PEARLS

- The plant anticancer alkaloids act on the microtubules, during the mitosis (M) phase of the cell cycle.
- The vinca alkaloids cause sensory and motor toxicities with the following order of activity: vincristine is greater than vinblastine, which is greater than vinorelbine.
- Neurotoxicity is dose limiting for vincristine, whereas myelosuppression is dose limiting for paclitaxel, etoposide, and methotrexate.

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CASE 51

A 45-year-old woman presents for the evaluation of a breast lump. She noticed the lump in her left breast approximately 3 months ago but didn't come in because she "thought it would go away." She denies pain, nipple discharge, or weight loss. Her last mammogram was 3 years ago. She has regular menstrual cycles. She is on no medications and has no significant medical history. On examination she is anxious, but her general examination is normal. Breast examination reveals a hard, 2-cm mass in the upper, outer quadrant of her left breast and several small lymph nodes in the left axilla. A stereotactic core needle biopsy of the mass confirms the diagnosis of ductal breast carcinoma. Further workup does not reveal distant metastases. She subsequently undergoes a lumpectomy and sentinel node biopsy. Pathology studies of the tumor reveal it to be estrogen- and progesterone-receptor positive, and she has microscopic metastases in the axillary lymph nodes. She is started on oral tamoxifen.

- What is the mechanism of action of tamoxifen?
- What are the side effects commonly associated with tamoxifen?

ANSWERS TO CASE 51:
Steroid Hormones and Antagonists

Summary: A 45-year-old woman with estrogen-receptor (ER)-positive breast cancer is begun on tamoxifen therapy.

- **Mechanism of action of tamoxifen:** Competitive inhibitor of estrogen receptors.
- **Common adverse effects:** Hot flashes, menstrual irregularities, sexual dysfunction, blood clots.

CLINICAL CORRELATION

Tamoxifen is a **selective estrogen receptor modulator (SERM).** It is a competitive inhibitor of estrogen binding to both isoforms of the estrogen receptor. This inhibits estrogen-dependent synthesis and autocrine growth-promoting actions of estrogen within the breast. Its primary use is as a chemotherapeutic agent in women with metastatic, ER-positive breast cancer. Although it is used in postmenopausal women, it is the first-line drug for treatment of ER-positive breast cancer in premenopausal women. Aromatase inhibitors are recommended for treatment of ER-positive breast cancers in postmenopausal women.

Tamoxifen is also used to reduce the incidence of breast cancer development in women who are at high risk for developing breast cancer as a consequence of genetic factors and family history. As an antiestrogen, tamoxifen causes menopausal side effects, predominantly hot flashes and vaginal dryness. It can cause menstrual irregularities in premenopausal women. Tamoxifen has an estrogen agonistic effect on other parts of the body. It may simulate the effect of unopposed estrogen on the endometrium, resulting in an increased risk of endometrial carcinoma; for this reason, tamoxifen is limited to 5 years. Similarly, tamoxifen, like estrogen, increases the risk of thromboembolic disease.

APPROACH TO:
Pharmacology of Antiestrogens

OBJECTIVE

1. Know the steroid hormone antagonists used in chemotherapy, their mechanisms of action, therapeutic uses, and adverse effects.

DEFINITIONS

Selective estrogen receptor modulators (SERMs): These are compounds that display a range of agonist-to-antagonist actions in a tissue-selective manner.

DISCUSSION

Class

Many breast cancers depend on the **proproliferative signals** produced by **estrogens** to support their growth. Similarly, the vast majority of **prostate cancers** depend on the effects of **androgens** to support their growth. This has given rise to a class of anticancer agents that interfere with the action of estrogens or androgens in particular tissues. The **SERMs** were developed in large part because of the understanding of the details of the molecular functioning of the estrogen receptor. There are **two forms of the estrogen receptor** (ER; see also Case 40) ERα and ERβ, which are derived from separate genes and have overlapping but distinct functions in a cell and promoter-dependent manner. Both ERs are weakly bound to the promoter/regulatory regions of genes that contain a particular DNA sequence, the estrogen response element (ERE). Binding of agonist, for example, 17β-estradiol, causes a significant and important change in the conformation of ER. This concept of ligand-mediated changes in receptor conformation is the key to the mechanism of action of the SERMs. The change in ER conformation causes ER to dimerize (ERα/ERα, ERβ/ERβ, or heterodimers of ERα/ERβ) and to bind more strongly to the ERE. One particular portion of the receptor, helix 12, is positioned and available to interact with other proteins called coactivators. Coactivators recruit other proteins of the RNA polymerase complex to the target gene(s) and produce the increase in transcription.

Ligands, such as the **SERMs** that are not pure agonists cause a different conformation of ER and these different conformations can interact with different coactivators. Estrogen antagonists cause a conformational shift in ER that facilitates the interaction with corepressors, proteins that reduce transcriptional activity from target genes. The effect of a given drug will depend on the nature of the compound, the ratio of ERα/ERβ, and the particular repertoire of coactivators and corepressors present in any given cell.

The **pharmacologic goal in the development of SERMs is to produce estrogenic actions in those tissues where it would be beneficial** (eg, bone, brain, liver) and to have either **no activity or antagonist activity in tissues, such as the endometrium or the breast, where estrogenic activity** (eg, proproliferative signals and increased risk of cancer) **might be deleterious.**

There are **three SERMs approved for use: tamoxifen, toremifene, and raloxifene;** several more SERMs are in various stages of clinical trials. **Tamoxifen** is a **triphenylethylene** derived from the estrogen agonist **diethylstilbestrol.** It binds to both ERα and ERβ. Tamoxifen has antiestrogenic, estrogenic, or mixed activity depending on the tissue and the target gene. Tamoxifen is an estrogen **antagonist in human breast** and ER-positive breast cancer cells. However, it has **agonist activity in the uterus** and stimulates proliferation in the endometrium. It has **estrogen agonist activity in the liver** where it causes a **decrease in total cholesterol and low-density lipoprotein (LDL) but does not increase triglycerides or high-density lipoprotein (HDL).** Tamoxifen is **antiresorptive in bone** and is very useful in the treatment of breast cancer. It is used alone or in combination with other agents for treatment of advanced breast cancer in ER-positive tumors and is indicated for both early and advanced cancer in women of all ages. Response rates are approximately

50 percent in tumors that are ER positive and nearly 70 percent in ER- and progestin-receptor-positive (PR-positive) tumors; response in ER-negative tumors is less than 10 percent. Tamoxifen reduces the risk of recurrence by approximately 50 percent. It is also approved for primary prevention in women at high risk of breast cancer; in clinical trials it caused a 50 percent reduction in invasive breast cancer and a 47 percent reduction in noninvasive cancers. **Treatment should be discontinued after 5 years because of the development of drug-resistant tumors. A 5-year course of aromatase inhibitors can be initiated subsequent to tamoxifen therapy.** The adverse effects of tamoxifen include hot flashes, nausea, and vaginal bleeding; more serious adverse effects include a two- to threefold increase in the risk of endometrial cancer and a twofold increase in the risk if thromboembolic disease. It may cause GI disturbances.

Tamoxifen is administered orally and a major metabolite produced in the liver is 4-OH tamoxifen, which has a 25- to 50-fold higher affinity for ERα and ERβ. Peak blood levels are attained 4–7 hours after administration. Tamoxifen is metabolized by the hepatic cytochrome P450 **system and excreted in the feces. Toremifene** is similar structurally to tamoxifen, with a chlorine substitution in one-ring structure. It has the same indications and effects as tamoxifen.

Raloxifene (see Case 40) is a benzothiophene that has been polyhydroxylated. Raloxifene has estrogen agonist activity in bone and inhibits resorption. It is indicated for the **treatment and prevention of osteoporosis.** Like SERMs, **progestin receptor modulators (PRMs)** and **androgen receptor modulators (ARMs),** which would have tissue-selective hormonal actions, are in clinical development.

Aromatase Inhibitors

Estrogens produced locally, that is, within a tissue, may play a significant role in breast cancer. This has greatly stimulated interest in the use of aromatase inhibitors to selectively block the production of estrogens. Current agents include both **steroidal** (eg, **formestane** and **exemestane**) and **nonsteroidal agents** (eg, anastrozole, letrozole, and vorozole). The **steroidal or type 1 agents** are **substrate analogs** that act as **inhibitors and irreversibly inactivate the enzyme,** while the nonsteroidal or type 2 agents interact reversibly with the heme group in the cytochrome P450 **moiety. Exemestane, letrozole, and anastrozole** are currently indicated for the treatment of breast cancer.

These agents may be used as first-line treatment of breast cancer (especially in postmenopausal women) or as second-line drugs after tamoxifen. They are **highly efficacious,** but unlike tamoxifen they **do not increase the risk of uterine cancer or venous thromboembolism.** Because they dramatically reduce circulating as well as local levels of estrogens, they **do produce hot flashes,** and there is concern about their long-term effects on bone and plasma lipid profiles. **Aromatase inhibitors are under investigation for the prevention of breast cancer.**

COMPREHENSION QUESTIONS

51.1 A 46-year-old woman is seen in your cancer clinic and concerned about her chances of developing breast cancer. Her mother died of the disease, and her sister has been diagnosed with the disease. A breast examination is negative. Should the patient's risk of breast cancer be high enough, which of the following might be used prophylactically in this woman?

A. Clomiphene
B. Leuprolide
C. Progesterone
D. Tamoxifen

51.2 A second year medical student is studying about the differences between estrogens and SERMs. As compared to 17β-estradiol, SERMs have which of the following properties?

A. They are active orally.
B. They are antagonists in all tissues.
C. They have tissue-specific effects.
D. They are more potent than 17β-estradiol.

51.3 A 44-year-old woman has developed breast cancer and is asked to participate in a clinical trial. She will be given formestane for 3 years. Which of the following are accurate statements about this medication?

A. It reversibly antagonizes the enzyme responsible for estrogen production.
B. It is a SERM similar to tamoxifen.
C. It is a nonsteroidal medication.
D. The patient will likely experience significant hot flashes.

ANSWERS

51.1 **D.** Tamoxifen may be used in woman at high risk to develop breast cancer. In general if the risk of developing breast cancer is 1.67 percent or higher over 5 years, then chemoprophylaxis is recommended. For instance a woman in her 40s without DVT and with a first-degree relative with breast cancer would be a candidate. This patient should have BRCA testing, since, if positive, more aggressive intervention such as mastectomy and oophorectomy should be offered. Leuprolide and clomiphene have antiestrogenic activities but are not used prophylactically in women at high risk of breast cancer. Progesterone may cause proliferation and cancer in the breast.

51.2 **C.** SERMs are agonists at estrogen receptors in some but not all tissues, and may have different agonist/antagonist effects in different regions of the body.

51.3 **D.** Formestane is a steroidal aromatase inhibitor that irreversibly inactivates the aromatase. Patients generally have significant hot flashes because of the low estrogen levels.

PHARMACOLOGY PEARLS

- Tamoxifen reduces the risk of hormonally responsive breast cancer recurrence by approximately 50 percent.
- Tamoxifen treatment should be discontinued after 5 years to avoid the development of drug-resistant breast tumors or uterine cancer.
- Aromatase inhibitors are highly efficacious, and unlike tamoxifen they do not increase the risk of uterine cancer or venous thromboembolism.

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CASE 52

A 22-year-old man is brought to the emergency room unresponsive and in respiratory distress. He was found unconscious at home next to a suicide note and an empty bottle of methanol. A brief history from an accompanying family member is significant for the patient having depression, but he is not currently on any medications. On examination he is not responsive to verbal stimuli but has pupillary and pain responses, and he is tachypneic and tachycardic (rapid respiratory and heart rates). His lungs are clear. You quickly institute supportive measures, intubate the patient, and send blood tests that confirm a profound anion-gap metabolic acidosis. No other drugs are found in his system. You diagnose him with an acute methanol overdose, start him on IV fluids, sodium bicarbonate, and an IV infusion of ethanol.

- What enzyme metabolizes methanol?
- What is the rationale for using ethanol to treat methanol toxicity?

ANSWERS TO CASE 52:
Solvent Toxicities

Summary: A 22-year-old man with methanol poisoning is being treated with IV ethanol.

- **Enzyme that metabolizes methanol:** Alcohol dehydrogenase.
- **Rationale for ethanol in methanol poisoning:** Competes for metabolism by alcohol dehydrogenase to reduce the production of toxic metabolites of methanol.

CLINICAL CORRELATION

The toxicity of methanol is primarily mediated by its metabolites. Methanol is metabolized by alcohol dehydrogenase to formaldehyde and subsequently to formic acid, the most likely cause of major organ toxicity. Formic acid inhibits cytochrome oxidase activity, resulting in tissue hypoxia and lactic acid production. The metabolic acidosis that occurs in methanol overdose is a result of the combination of formic acid and lactic acid that is produced. The most characteristic symptom in methanol poisoning is visual disturbances with blurred vision and a sense of "being in a snowstorm." Isopropyl alcohol and ethylene glycol similarly are metabolized by alcohol dehydrogenase to toxic metabolites. Unfortunately, the toxic metabolites of all of these solvents can cause permanent neurologic damage, blindness, coma, and death. In these clinical settings ethanol can be used therapeutically. It is given by continuous IV infusion to compete for metabolism by alcohol dehydrogenase. With hemodialysis, this can help to reduce the ongoing production of toxins. Sodium bicarbonate can be given to help correct the metabolic acidosis. Fomepizole, another available, very costly (~$4000 per patient) inhibitor of alcohol dehydrogenase is also available.

APPROACH TO:
Pharmacology of Solvent Toxicity

OBJECTIVES

1. Outline the basic principles of toxicology, including the dose-response relationship and risk and duration of exposure to toxins.
2. List the classes of solvent toxins and describe how exposure occurs and the effects of exposure.

DEFINITIONS

Toxicology: Study of the deleterious effects of chemical, biological, and physical substances, including their deleterious effects on the human body.

Xenobiotics: Deleterious foreign substances.

Toxicokinetics: Study of the absorption, distribution, metabolism, and elimination of xenobiotics.

DISCUSSION

Class

In considering the human toxicity of xenobiotics, it is important to keep in mind the following general principles:

The **toxicokinetics of xenobiotics** is equivalent to the pharmacokinetics described for drugs used as therapeutic agents.

Exposure to toxic substances is generally either **occupational** or **environmental** (air, soil, water, etc).

Certain xenobiotics (eg, acids, alkali, strong reducing and oxidizing agents, detergents) **cause nonspecific damage** to tissues by altering proteins, nucleic acids, lipids, and other macromolecules that are integral to cell structure and integrity.

Biotransformation of **chemical toxicants** may result in formation of **reactive metabolites** or the production of **free radicals and reactive oxygen** that form covalent bonds with proteins, nucleic acids, and lipids to disrupt cell function.

For many xenobiotics, a **dose-response relationship** for toxicity cannot be directly determined from human data but rather must be based on data derived strictly from **animal studies.**

In addition to decreasing or eliminating exposure, management of the poisoned patient is supportive and depends on the specific tissue or organ or tissue involved (Table 52–1).

Table 52–1 • SOLVENT CLASSIFICATION AND TOXICITY

Selected Solvent Classes*	Selected Toxicity
Aliphatic alcohols (eg, methanol)	See clinical correlation
Aliphatic hydrocarbons (eg, hexane)	CNS depression, sensorimotor disturbances
Glycols and glycol ethers (ethylene glycol, propylene glycol, etc)	CNS depression, renal and hepatic toxicity
Halogenated aliphatic hydrocarbons (eg, chloroform, carbon tetrachloride, trichloroethylene, tetrachloroethylene, 1,1,1-trichloroethane)	CNS depression, impaired memory, *tetrachloroethylene:* peripheral neuropathy *Carbon tetrachloride* (acute or chronic exposure): hepatic injury *Chloroform, carbon tetrachloride, trichloroethylene:* renal injury carcinogenicity in animals (certain halogenated hydrocarbons)
Aromatic hydrocarbons (eg, benzene, toluene)	*Benzene:* CNS depression that may result in ataxia, vertigo, and coma. Chronic exposure can result in severe bone marrow depression and possibly leukemia *Toluene:* CNS depressant that acutely can cause ataxia at low exposure and at high exposure lead rapidly to loss of consciousness. The effects of chronic exposure are uncertain

*These agents are used as industrial solvents, as cleaning agents, in synthesis of other chemicals, or as components of personal and household products.

COMPREHENSION QUESTIONS

52.1 Which of the following is the most characteristic symptom in methanol poisoning?

A. Carcinogenicity
B. Hepatic injury
C. Renal injury
D. Visual disturbances

52.2 A 45-year-old alcoholic male is brought into the emergency department due to ingestion of wood alcohol (methanol). Which of the following compounds is the most likely cause of organ toxicity from methanol?

A. Formaldehyde
B. Formic acid
C. Lactic acid
D. Methanol

52.3 A 34-year-old lab technician has been noted to have anemia, low white blood cell count, and thrombocytopenia. Severe bone marrow depression is most likely to result from exposure to which of the following solvents?

A. Benzene
B. Ethylene glycol
C. Hexane
D. Toluene

ANSWERS

52.1 **D.** The most characteristic symptom in methanol poisoning is visual disturbances. Hepatic injury, renal injury, and potential carcinogenicity are more characteristic of the halogenated aliphatic hydrocarbons overdose.

52.2 **B.** Methanol is metabolized by alcohol dehydrogenase to formaldehyde, which is then metabolized to formic acid, the most likely cause of methanol's organ toxicity. Formic acid inhibition of cytochrome oxidase activity results in tissue hypoxia with the production of lactic acid, which with formic acid, can result in metabolic acidosis.

52.3 **A.** Chronic exposure to benzene can result in bone marrow depression. Exposure to toluene results in CNS depression. The effects of chronic exposure to toluene are uncertain. Hexane is more likely to cause CNS depression and sensorimotor disturbances. Ethylene glycol is likely to cause CNS disturbances and renal disturbances.

PHARMACOLOGY PEARLS

- Toxicity from the solvents commonly affect the CNS, causing sedation or CNS depression.
- Exposure to carbon tetrachloride can lead to hepatic toxicity.
- Chronic exposure to benzene may lead to bone marrow depression and possibly leukemia.
- Regional poison control centers are available 24 hours a day (1-800-222-1222) to assist with treatment of the poisoned patient.

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CASE 53

A woman brings her 5-year-old son into your office for evaluation. He has had progressive difficulty walking in the past few months and has seemed irritable. He has also seemed quite tired. He has vomited on one or two occasions over the past week. His past medical history is unremarkable. He was born after an uncomplicated, full-term pregnancy. He has had all of his vaccines and has achieved all of his developmental milestones for his age. He lives with his parents in a home that was built in the 1920s, which they have been renovating. On examination, the child is somewhat restless but cooperative. His conjunctiva and mucous membranes are pale. Neurologic examination is significant for an ataxic gait (clumsiness). His general examination is otherwise unremarkable. A complete blood count (CBC) shows him to be anemic. A serum lead level is markedly elevated. You admit him to the hospital and start him on dimercaprol and ethylenediaminetetraacetic acid (EDTA).

- How does chronic lead exposure cause anemia?
- What is the mechanism of action of dimercaprol and EDTA?

ANSWERS TO CASE 53:
Heavy Metal Poisoning

Summary: A 5-year-old boy with lead toxicity is admitted to the hospital and started on dimercaprol and EDTA.

- **Mechanism of lead-induced anemia:** Inhibition of δ-aminolevulinic acid dehydratase, which blocks the conversion of δ-aminolevulinic acid to porphobilinogen, disrupting hemoglobin synthesis.
- **Mechanism of action of dimercaprol and EDTA:** Dimercaprol and EDTA increase the excretion of heavy metals by chelation, which forms soluble substances that can be excreted.

CLINICAL CORRELATION

Most lead toxicity in children is a result of GI ingestion. Children absorb a greater portion of ingested lead than adults do. The source of this lead is often from lead-based paint that was widely used before the 1970s. Inorganic lead binds to hemoglobin and distributes to soft tissues, including the brain. It later accumulates in the bone, from which it is eliminated very slowly. Lead produces anemia via the inhibition of the enzyme δ-aminolevulinic acid dehydratase, which converts δ-aminolevulinic acid to porphobilinogen. This interrupts the pathway of synthesis of hemoglobin. Lead can also cause CNS effects, especially in children. Common signs include vertigo, ataxia, headache, restlessness, and irritability. Vomiting, delirium, and seizures may occur. Lowered IQ and behavioral disturbances may be the result of childhood exposure. Peripheral neuropathy is another possible outcome of chronic lead poisoning.

Treatment of lead toxicity requires cessation of exposure and, in severe cases, chelation therapy. In children, dimercaprol and EDTA are the first-line drugs of choice frequently used. Calcium disodium edentate is administered intravenously or intramuscularly; dimercaprol is given intramuscularly. These drugs are chelators, which bind lead, forming soluble compounds that are excreted in the urine. Other drugs used for chelation include succimer, calcium disodium EDTA, and penicillamine.

Lead screening is a required component of well child exams. In addition to serum lead testing, questionnaires are also done to assess for exposure in the environment or food. Common sources include foreign candies, home remedies for abdominal pain, paint in old homes, family member's occupational exposure, and cooking in foreign-made pots.

APPROACH TO:

Pharmacology of Heavy Metal Poisoning

OBJECTIVES

1. Discuss the general principles related to heavy metal poisoning.
2. List the common sources of heavy metal exposure and describe their mechanisms of action and their toxicities (Table 53–1).
3. List agents used for the management of heavy metal poisoning and describe their mechanisms of action.

DISCUSSION

Class

The general principles related to heavy metal toxicity are the following:

Exposure to heavy metals may be **acute or chronic,** generally through accidental occupational or environmental exposure.

Most, if not all, heavy metals **interact with sulfhydryl groups** and perhaps other functional groups of cell proteins to cause their toxicity.

Multiple organ systems may be affected but particularly the **CNS, liver, kidney, and respiratory and immune systems.**

Management of metal poisoning involves **removal of the source, decontamination,** and **supportive treatment for symptoms.** In addition, **metal chelators** can be used to remove or prevent metal binding to important cell constituents (Table 53–2). The major chelators interact with the same functional groups as the heavy metals to form complexes that can then be eliminated from the body. With the exception of **deferoxamine,** their selectivity is relatively poor in that they **also bind important endogenous divalent cations, notably Ca^{2+}.**

Table 53–1 • HEAVY METALS AND TOXIC EFFECTS

Heavy Metal	Toxicity	Notes
Iron (Fe)	GI mucosa destruction, with severe gastroenteritis, abdominal pain, and bloody diarrhea, with subsequent endothelial damage in the liver and kidney that can result in metabolic acidosis, coma, shock, cardiovascular collapse, and death. Primary tissue damage occurs through free radical formation and lipid peroxidation.	Exposure in children is generally by accidental ingestion of iron supplements. In adults toxicity is generally the result of repeated transfusions, inherited disorders, or intentional overdosing. Important to verify iron deficiency anemia prior to giving iron supplementation. Also important to re-verify iron studies and CBC prior to refills on iron sulfate.
Mercury (Hg)	Neurologic and behavioral changes, including visual deficits, because of neuronal injury and encephalopathy are among the most common adverse effects. Excitability, tremors, and gingivitis are hallmarks of mercury toxicity. GI and renal injury are common with exposure to mercury salts, which can also cause severe pain and vomiting because of its corrosive action on the mucosa of the mouth, pharynx, and intestine. Mercury vapor can result in severe respiratory difficulty with residual fibrosis	Elemental mercury vapor is well absorbed from the lungs. Elemental mercury in liquid form is relatively nontoxic. Inorganic mercury salts are generally ingested and when absorbed concentrate in the kidney. They have a long half-life. Organomercury compounds are absorbed readily from the GI tract. They undergo enterohepatic recycling with long half-lives. The developing nervous system is especially vulnerable to mercury exposure in utero. The major source of mercury poisoning is contaminated fish
Arsenic (As)	Acute: develops in minutes to hours. GI issues, nausea, vomiting, watery diarrhea Garlic odor of breath. Cardiac arrhythmias, Acute respiratory distress syndrome, headache, Confusion and memory problems. Chronic: skin lesions, peripheral neuropathy	Exposure can be through ingestion or inhalation
Lead (Pb)	Acute: uncommon; includes paresthesia, muscle weakness, hemolysis, renal damage Chronic: see Clinical Correlation; most serious toxicity is encephalopathy that can lead to impaired learning and mental retardation, especially in children	See Clinical Correlation. Crosses placental barrier and can cause in utero damage leading to impaired CNS development

Table 53–2 • HEAVY METAL CHELATORS

Heavy Metal Chelators	Primary Metals Chelated	Notes
Dimercaprol	Lead (Pb), mercury (Hg), arsenic (As)	Administered parenterally; avoid in iron or cadmium poisoning because complex is extremely hepatotoxic; avoid with methylmercury poisoning because it facilitates entry into the CNS. Avoid use in persons with peanut allergy as is dissolved in peanut oil
EDTA	Lead (Pb)	Administered parenterally; chronic treatment requires "off" periods to allow redistribution out of bone. Use after dimercaprol as only removes lead from extracellular compartment and may increase CNS lead levels
Deferoxamine	Iron (Fe), aluminum (Al)	Administered parenterally
Penicillamine trientine	Copper (Cu), adjunct for Pb, Hg	Administered orally; used to chelate excess copper in Wilson disease; may result in allergic reaction
Succimer	Lead (Pb), adjunct for Hg, As	Administered orally; causes GI disturbances and rash

COMPREHENSION QUESTIONS

53.1 A 4-year-old child is suspected of having lead poisoning from paint from an old building. Which of the following heavy metal chelators is used as a primary treatment for mercury poisoning?

A. Dimercaprol
B. EDTA
C. Penicillamine
D. Succimer

53.2 A 3-year-old girl is brought into the emergency department for possible heavy metal poisoning. The child has severe gastroenteritis, abdominal pain, and bloody diarrhea. Which of the following heavy metals is most likely the cause of this child's symptoms?

A. Arsenic
B. Elemental liquid mercury
C. Iron
D. Lead

53.3 A 2-year-old toddler is noted to have a hemoglobin level of 9 g/dL (anemia), likely from pica (eating the dirt around a battery plant). A peripheral smear indicates some basophilic stippling of red blood cells. Serum lead levels confirm lead poisoning. Lead-induced anemia is a result of inhibition of which of the following enzymes?

A. Aldehyde dehydrogenase
B. Cytochrome oxidase
C. δ-Aminolevulinic acid dehydratase
D. Monoamine oxidase

ANSWERS

53.1 **A.** Dimercaprol is used as a primary heavy metal chelator for treatment of mercury poisoning. EDTA and succimer are used for lead poisoning. Penicillamine is used to treat copper poisoning. EDTA and penicillamine are used as adjuncts to treat mercury poisoning.

53.2 **C.** Iron poisoning causes characteristic GI mucosa destruction, with severe gastroenteritis, abdominal pain, and bloody diarrhea. Elemental liquid mercury is relatively nontoxic. A nonspecific GI, CNS, and cardiovascular toxicity is caused by arsenic. The most serious (chronic) toxicity from lead poisoning is encephalopathy.

53.3 **C.** Lead produces anemia via the inhibition of the enzyme δ-aminolevulinic acid dehydratase, which converts δ-aminolevulinic acid to porphobilinogen. This interrupts the pathway of synthesis of hemoglobin.

PHARMACOLOGY PEARLS

- Iron toxicity can lead to gastroenteritis, liver, and kidney damage and, if severe enough, death.
- The most common manifestations of mercury poisoning are the neuronal toxicity such as visual deficits.
- Lead poisoning can lead to mental retardation in the developing fetus or children.
- Regional poison centers are available to assist with treatment (1-800-222-1222).

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CASE 54

A healthy 25-year-old woman with no significant past medical history or surgical history presents for a routine well woman examination. She is a G2P2002, married, nonsmoker who desires to discuss contraceptive options. She does desire to become pregnant again but not in the near future. She denies any prior sexually transmitted infections (STIs) and has no significant medical concerns or complaints.

- What are the long-acting reversible contraceptive (LARC) agents ?
- As compared to oral contraceptive (OC) agents, what are the advantages of LARC agents?
- What are the mechanisms of action of the types of LARCs?

ANSWERS TO CASE 54:
Contraceptive Management

Summary: A 25-year-old female without medical problems or complaints who desires long-term but reversible contraception

- The LARC category of contraceptives include IUD (copper vs. Mirena—progestin based), hormone injections (progesterone based), and subdermal implants such as Implanon (progestin based).
- An advantage of LARC over OCP (oral contraceptive pill) is that they do not have to be taken daily by the patient and as such often results in higher typical use efficacy.
- The LARC agents are either progestin based or copper based. The mechanism of action for the progesterone only products (Implanon, Depo-Provera injection, Mirena IUD) are to suppress ovulation and make the cervical environment less favorable for sperm survival/transport and endometrial implantation. The copper IUD functions as a spermicide (inhibits sperm motility/transport/acrosomal enzyme action and prevents fertilization of the ovum.

CLINICAL CORRELATION

The choice of contraception depends on a variety of factors. In some cases the risk of comorbidities may limit the options. At times the choice is dependent on logistics of how often the contraceptive has to be used. Duration of desired contraception is another key factor in choosing the right contraceptive for a given patient. In patients who prefer concurrent STI prevention, barrier methods would be ideal. In patients who no longer desire fertility, surgical options may be suggested. A thorough medical/surgical/social history along with a full review of systems should be done prior to initiation of contraception to offer a customized method for the patient. Some of the contraceptives may offer other noncontraceptive benefits (discussed later). Cost is another factor in choosing contraceptives. Often, minor side effects will abate in a few months, so having this discussion with the patient in the beginning may minimize confusion and frustration.

If unprotected sex occurs and pregnancy is not desired, emergency contraceptives are readily available and are a viable option. However, the patient must be informed that this method should not be the sole contraceptive management, nor should it be used in preventing STIs.

APPROACH TO:
Contraceptive Agents

OBJECTIVES

1. Discuss the categories of various contraceptive options and their respective mechanisms of action.
2. Discuss the noncontraceptive uses for the various agents.
3. Discuss the risks and benefits of the agents.
4. Address issues pertaining to emergency contraception

DEFINITIONS

Contraception: Intentional prevention of pregnancy via the use of various agents/devices/sexual practices/surgical procedures by interfering with any or several of the following processes: implantation, fertilization, ovulation.

Emergency contraception: Using contraception after unprotected intercourse—consensual or nonconsensual—to prevent pregnancy.

DISCUSSION

Note that this case will not address all the available options for contraception. For a full discussion on all the options (natural family planning, hormonal agents, surgical techniques, barrier methods) refer to the Family Medicine and/or Obstetrics and Gynecology Case Files (see also Table 54-1 for contraception options).

CLASSES OF AGENTS

Oral Contraceptive (OC) Agents

All oral contraceptive agents are hormonal agents, but differ in that they can either be a combination of estrogen/progestin or be a progestin only. Most of the OCPs contain the combination, although there are a few that have only progesterone. The extended duration contraceptive pills also contain combination of estrogen and progesterone.

The estrogen component is typically ethinyl estradiol, whereas the progesterone may vary and is usually either a first, second, third, or fourth generation (pregnanes, estranes, gonanes, or drospirenone products, respectively). The combination OCPs can vary in their dosing strength of the individual components, whereas all the other options have fixed dosing. The ethinyl estradiol may commonly come in the following strengths: 20, 25, 30, 35 micrograms. The progesterone dose varies based on the individual component used. The combination OCP may also come as monophasic or biphasic/triphasic options—the latter two where the individual components vary in their dose based on the day to reflect the physiologic variations. The monophasic

Table 54–1 • Contraceptive Options

Option	Active agent	Duration	Cost
LARC 1. DMPA 2. IUD (Mirena vs. copper) 3. Implanon	 1. Progestin 2. Progestin vs. copper 3. Progestin	 1. 3 months 2. 5 vs. 10 years 3. 1 years	 1. $55/3 months 2. $300-$700/5-10 years 3. $400-$800/annually
OC Agents 1. Combination 2. Progestin 3. Emergency	 1. EE/Progestin 2. Progestin 3. Progestin	 1. Daily 2. Daily 3. Use 24-120 hours post intercourse	 1. $9-$50/month 2. $35-$50/month 3. $50 per package
Barrier	No hormone	Daily	Varies on frequency of intercourse and type used. $10–$50 per package
Permanent 1. Vasectomy 2. Adiana/Essure 3. BTL	N/A	Permanent	 1. $350 2. $2000-$3000 3. $2000-$4000
Transdermal (Ortho Evra) Intravaginal (NuvaRing)	EE/Progestin	1 week 3 weeks	$55-85 $55-$85

options have less menstrual irregularities in general. Nausea, headaches, elevated blood pressure, weight gain, decreased libido, and dyslipidemia may occur with the estrogen component but often can be diminished by decreasing the dose of estrogen or with continued use. Due to the EE component, there is also a low risk of venous thromboembolism (VTE) and cardiovascular disease that is increased in smokers (especially those who smoke >15 cigarettes daily) or women above the age of 35. These risks are less than 1 percent. The possible association with breast cancer in estrogen containing products is also low (<1%). The World Health Organization (WHO) has categorized the precautions and contraindications to OCP use into four categories. Some of the noncontraceptive benefits of using combination estrogen/progesterone products include reduction in ovarian and endometrial cancer, improvements in acne, dysmenorrhea, menorrhagia, metrorrhagia, and functional cysts. For progesterone-based products, the main adverse events include risk for hirsutism, acne, menstrual irregularity, and spotting. There are also concerns of weight gain and decreased bone mineral density with continued use. The progestin-only pills are also less effective than the combination OCPs (0.5% vs. 0.1% failure rate of progestin only vs. combination OCP with perfect use or 1% to 3% failure rate for either product with typical use) and also have less flexibility in timing. The oral agents have many interactions that can affect the effectiveness of the OCP or the other medication.

Mechanism of Action

The estrogen component inhibits ovulation by suppressing LH and FSH and prevents implantation. The progesterone component inhibits ovulation by suppressing LH, thickens cervical mucus, and thins the endometrial lining thereby preventing sperm transport and implantation.

Administration

The OCPs (combination and progestin-only pills) are taken orally around the same time each day. The progestin-only pills have less flexibility (need to be taken within an hour of the time daily, whereas the combination pills may be taken within 3 hours of the daily time). The OCPs come in a pack of 21 active pills and 7 placebo pills. With the use of the placebo pills, the patient will start her withdrawal bleed. If a patient prefers to limit her menses then she can opt to just take the active pills continuously or use a marketed extended use agent. Seasonale and Seasonique are two commercially marketed extended duration OCPs. Despite patient concerns, this approach is effective and has not shown evidence of increased harm. Patients may customize when they have their menses as well by when they start the OCP pack; for example, starting on a Sunday would in theory eliminate menses on weekends. Emergency contraception at present is marketed as an oral tablet (progestin based) that can be taken either as 2 tablets at once or each one 12 hours apart—Plan B. A new option, Ella (a progesterone agonist/antagonist) is a single 30-mg tablet that is reportedly effective up to 5 days post intercourse. Apart from this, many commercially available OCPs can be used for emergency contraception by altering the amount of pills taken. This form is most effective if taken immediately after, but success rates are still high 24–120 hours post unprotected intercourse.

Pharmacokinetics

Due to the lipophilic nature of the estrogens and progestins, these drugs are readily absorbed following oral administration. The ethinyl substitution on 17β-estradiol inhibits first-pass hepatic metabolism. Estrogens undergo enterohepatic recirculation, which depends in part on hydrolysis of hepatic conjugates in the gut by bacterial enzymes. Antibiotic treatment can reduce effectiveness of OCP or HRT (Hormone Replacement Therapy). Several medications may interact with OC agents.

Transdermal and Intravaginal Agents

Currently available transdermal (Ortho Evra) and intravaginal (NuvaRing) contraceptives are both combination estrogen/progestin products. These agents provide a more consistent delivery of the hormones and permit a lower dose than oral preparations. The intravaginal product, NuvaRing, is placed into the posterior fornix of the vagina, left in place for 3 weeks, and removed for 1 week. The transdermal product (Ortho Evra) is placed on the buttock/upper torso/abdomen/upper arm weekly and changed once a week for 3 weeks, with the 4th week being a patch-free period. The Ortho Evra patch is restricted to patients less than 198 pounds due to decreased effectiveness in patients above this weight. The efficacy, mechanism of action, benefits, and risks are comparable to the combination OC agents. These agents also have the same noncontraceptive benefits as the combination OC agents. Local skin or mucosal irritation may occur with either of these options but are not typical.

Barrier Methods

Commonly available barrier methods include male and female condoms, diaphragm, cervical caps, and contraceptive sponges. Neither the condoms nor contraceptive sponges require a prescription. These agents have fewer side effects than hormonal contraception and have the dual benefit of contraception and STI prevention. Additionally, if a double barrier is used (eg, condom + vaginal spermicide or diaphragm + condom), efficacy increases substantially. The major issue with these options is compliance with use as they are only effective if a new product is used at each episode of intercourse. Oral condoms are also available to provide additional protection. Another drawback of this method is the possibility of improper placement or breakage in which case both contraception and STI prevention are compromised. Local skin or mucosal reactions are usually uncommon.

Long–Acting Reversible Contraceptive (LARC) Agents

LARCs commonly used in the United States include medroxyprogesterone acetate (Depo-Provera as the Brand) progesterone acetate injections (DMPAs), Mirena (progestin based) IUD, Implanon (progestin based) subdermal agent, and copper IUD. DMPA is an injectable progesterone-based contraceptive that is given intramuscularly or subcutaneously (Depo-sub QProvera 104) every 3 months. Its efficacy is higher than the oral progestin mainly due to the fact that patients do not have to take the medication daily. DMPA is administered subcutaneously (SQ) and has been available since 2010. It uses 30 percent less hormone, is less painful, has similar efficacy, and has had success for self-administration by the patient in several trials. The predominant adverse effects of DMPA (SQ and IM) include weight gain of 3.5 to 5 pounds in the first year and menstrual irregularity/amenorrhea. There are also long-term concerns of decreases in bone mineral density with the use of any progesterone-only contraceptive agent. Intrauterine devices are typically inserted as an office procedure while the patient is on her menses and is to be removed in 5 or 10 years. The Mirena IUD (5-year product) has the same benefits/risks/mechanism of action as the other progestin-based products. The Mirena IUD may also be used for emergency contraception. The copper IUD (10-year product) functions essentially as a barrier agent and as a spermicide (inhibits sperm motility/transport/acrosomal enzyme action) and prevents fertilization of the ovum. Most common side effects include increased dysmenorrhea or increased menstrual flow for the first few months. The intradermal product (Implanon) is inserted as an office procedure subdermally into the medial aspect of the upper arm and removed in 1 year or 3 years depending on the product used. Implanon has the same mechanism of action/benefits/risks as the other progestin-only products.

Permanent Contraception

For women and their partners who desire permanent sterility, currently available options include bilateral tubal ligation, vasectomy, hysterectomy (if other indications), and fallopian tube obstruction methods (Essure and Adiana). Vasectomy is an office procedure that can be done in the primary care or specialist office and requires only local anesthesia. The procedure often takes 30 minutes to complete but requires the male to submit semen samples until sterility is assured (typically

6 weeks). Although reversal may be possible depending on the technique used initially, patients should be counseled that this is a permanent procedure. Bilateral tubal ligation is an operative procedure done under general anesthesia in the operating room. This may be reversed, but generally is considered a permanent procedure. Essure and Adiana are permanent sterilization techniques in which silicone coils are inserted into the fallopian tubes, which eventually lead to permanent scarring/occlusion of the area and offer permanent sterilization. This procedure is typically done via an office procedure and requires a separate procedure termed hysterosalpingogram (HSG) for placement and for verification. Once the procedure success has been verified (typically 3 months), sterility is fairly assured.

COMPREHENSION QUESTIONS

54.1 A 32-year-old female G1P1001 presents to address problems with her combination OCP. She has noticed increased breakthrough bleeding and spotting over the past few months. She is still having regular menses and denies any other complaints and is happy with the type of contraception. Which of the following would be your next step?

A. Provide drug-free period for 1–2 months
B. Switch to progestin-only pill
C. Increase the progesterone component of the combination OCP
D. Increase the estrogen component

54.2 A 37-year-old morbidly obese female G6P6006 who is married, monogamous, presents to address contraceptive options. At present she does not desire fertility for several years. She has no past medical or surgical history, but does smoke two packs per day. Which of the following options would be least preferred in this patient?

A. Ortho Evra transdermal patch
B. Mirena IUD
C. Depo-Provera injection
D. Progestin-only pill

54.3 A 24-year-old nulliparous female with no past medical history presents to discuss contraception. She has a history of acne and painful menses since menarche. She has regular menses now and uses condoms for STI prevention. The patient's biggest concern is not to have unexpected spotting, intermenstrual bleeding, or irregularity of her cycles as this would negatively affect her sex life. Which of the following options would be best for this patient?

A. Progestin-only pill
B. Implanon intradermal implant
C. Mirena IUD
D. Combination monophasic OCP

ANSWERS

54.1 **D.** As the patient is happy with the type of contraceptive, the preference should not be to change to a difference modality. Simply increasing the estrogen component will typically help reduce the irregularity and intermenstrual bleeding.

54.2 **A.** Obese patients over 198 pounds typically have much less success with the Ortho Evra patch. In addition as the patient is over the age of 35 and a heavy smoker (over 15 cigarettes daily), it would be prudent to avoid any contraceptive containing estrogen to diminish the cardiovascular and VTE risks. All of the other choices would provide adequate contraception without the above risks as they are all progesterone-only options. As the patient desires contraception for several years, the Mirena IUD would be ideal in this patient.

54.3 **D.** Acne and dysmenorrhea (painful menses) can be improved with combination OCPs. The progesterone-only options (which include choices a–c) could worsen acne and have a much higher risk of irregular menses, intermenstrual bleeding, and spotting. In addition, they are less effective for dysmenorrhea than the combination OCPs. Monophasic combination OCPs are generally better than biphasic or triphasic combination OCPs in regulating menses.

PHARMACOLOGY PEARLS

- Progesterone-only contraceptives offer the advantage of not increasing VTE or cardiovascular risks compared to combination estrogen/progesterone agents.
- Combination estrogen/progesterone products help with acne, dysmenorrhea, as well as menstrual irregularities, and have been associated with a decrease in ovarian and endometrial cancers.
- Contraceptive choice should be based on patient preference, risk of comorbidities, desired duration of contraception, cost, and avoidance of contraindications.
- LARC agents have higher typical use efficacy than the other agents due to decreased need for daily patient compliance.

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CASE 55

A 48-year-old Caucasian woman you have been treating for several years comes to your family medicine practice and seems embarrassed. She complains of urinating at least 10 times a day and 3 to 4 times at night and states it is interfering with her business and social life. She indicates her problem, which she says is "due to her getting older," began about 2 years ago. She has tried several things to help, including drinking only one cup of coffee in the morning and total avoidance of liquid after 6 PM. She has begun wearing pads to avoid the embarrassment of leakage. She describes being in an important business meeting and having to get up and leave to go to the bathroom. She constantly worries about the location of the nearest bathroom and has avoided social events like her son's soccer games, which are on an open field with no facilities. Upon further questioning she denies leakage with coughing, sneezing, or laughing. She denies any dysuria, hematuria, or feeling of incomplete voiding. She is monogamous without any prior history of sexually transmitted infections (STIs). You assure her the problem is not due to "getting old" and that there are treatable medical causes for the problem. Your physical examination is negative for STIs, vulvar or vaginal inflammation/infection/trauma, and cystocele. You order a urinalysis which comes back normal. You prescribe a trial of oxybutynin.

- What are the causes of overactive bladder?
- What is the mechanism of action of oxybutynin?
- What are the different classes of agents used in the treatment of the different kinds of urinary incontinence?

ANSWERS TO CASE 55

Urinary Incontinence

- Urge incontinence (see below for other forms of UI) is caused by contraction of the bladder such that urine passes the urethral sphincter at the wrong time.
- Oxybutynin is an anticholinergic drug that blocks muscarinic cholinergic receptors. M3 cholinergic receptors are responsible for the direct activation of the detrusor muscle. Oxybutynin decreases frequency of symptoms, and delays initial desire to void.

CLINICAL CORRELATION

There are several types of urinary incontinence and they have different causes. **Urge incontinence** as described in this case is typified as urinating more than eight times a day accompanied by a sudden and intense urge to urinate, frequently followed by involuntary loss of urine. The detrusor muscle contracts well before the bladder has filled and may give a warning of only a few seconds before the bladder sphincter muscle relaxes. The fundamental problem seems to be neuromuscular in origin. Contraction of the detrusor muscle is mediated by M3 cholinergic receptors. Urge incontinence may be caused by urinary tract infections, bladder irritants, bowel disease, Parkinson disease, Alzheimer disease, stroke, or nervous system damage associated with multiple sclerosis. If there's no known primary cause, urge incontinence is also called overactive bladder.

Stress urinary incontinence (SUI) occurs upon sneezing, laughing, coughing, or other maneuvers that increase intra-abdominal pressure in the presence of a weakened bladder sphincter. Urethral pressures, prolapse conditions, and congenital and acquired sphincteric dysfunction all contribute to SUI pathophysiology. In women, childbirth, pregnancy, and menopause can cause stress incontinence; in men, prostate removal is a cause.

Overflow incontinence is a frequent near-constant loss of urine caused by inability to void. This usually has an anatomical or neural cause that interferes with normal emptying of the bladder. **Mixed incontinence** refers to a combination of types. The most common type of urinary incontinence in older women is a mixture of urge and stress incontinence. Treatments include lifestyle and behavioral modifications, drugs, and surgery.

Often the detailed history and examination is sufficient to give a presumptive diagnosis; however, various testing may be needed to rule out other contributing or causative etiologies. On occasion diagnostic testing, radiographic testing, and laboratory testing may be required as well.

APPROACH TO:

Pharmacology of Agents that Act on the Urinary Tract

OBJECTIVES

1. List the drugs that are used in cases of urinary incontinence.
2. Describe the mechanism of action, route of administration, and adverse effects of these drugs.

DEFINITIONS

Urinary incontinence is the inability to control urine flow. It can be associated with decreased quality of life and social withdrawal. Elucidating the type of urinary incontinence guides management.

DISCUSSION

Urinary incontinence affects 10 to 70 percent of women depending somewhat on ethnicity, and prevalence increases with age. Annual medical costs are estimated at over $16 billion, which exceeds breast and ovarian cancer combined.

Class

Pharmacologic treatment depends on the type of urinary incontinence. Conservative management of urge incontinence includes behavioral techniques and lifestyle changes. Behavioral techniques include pelvic floor muscle training (PFMT, Kegel exercises), vaginal devices, and bladder training; lifestyle modifications include weight management; reducing alcohol consumption, smoking, and caffeine; and liquid intake reduction. A mainstay of pharmacologic management is **anticholinergic therapy**. The bladder contraction is controlled mostly by M2 and M3 muscarinic cholinergic receptors, and the direct contraction of the detrusor muscle via M3 receptors is most important. First-line agents include **oxybutynin and tolterodine**, and if these are ineffective solifenacin, trospium, darifenacin, fesoterodine, and tropantheline may be used. Oxybutynin has some specificity for M3 cholinergic receptors but also blocks M2 and M1, all of which are present in the bladder. Tricyclic antidepressants such as imipramine can be used if anticholinergics fail. A combination of tricyclics in conjunction with oxybutynin may be used cautiously for a synergistic effect.

Tolterodine, solifenacin, arifenacin, and fesoterodine are "second-generation" antimuscarinics with reduced central nervous system penetration and have better selectivity for the M3 subclass of acetylcholine receptors, resulting in improved tolerability. Tolterodine is better tolerated than oxybutynin with less moderate-to-severe dry mouth and fewer dropouts because of medication side effects but is not as effective.

Solifenacin in another antimuscarinic that has proven effective in patients with urge incontinence who have not responded to tolterodine or oxybutynin. It has a long elimination half-life that permits once-a-day dosing.

For stress incontinence caused by urethral sphincter insufficiency, the first-line pharmacologic therapy is pseudoephedrine, if there are no contraindications. Tricyclics such as amitriptyline or imipramine can be useful in mild or moderate cases. Although the cure rates are low, subjective improvement rates are moderate. This is also useful in patients who are considered a high surgical risk. Estrogen can be used as an adjunct in postmenopausal women with stress incontinence. There are many surgical procedures that have been developed for urinary incontinence. Most act to support the function of the urinary sphincter.

Structure

Oxybutynin is a tertiary amine. It supplied as a mixture of the (R)- and (S)-enantiomers; the (S)-enantiomer has little anticholinergic activity.

Adverse Effects

Common adverse effects associated with oxybutynin and other antimuscarinic anticholinergics include dry mouth, difficulty in urination, constipation, blurred vision, drowsiness, and dizziness. Anticholinergics have also been known to induce delirium. Dry mouth may be particularly severe especially with oxybutynin; one estimate is that 25 to 50 percent of patients who begin oxybutynin treatment may have to stop because of dry mouth. *N*-Desethyloxybutynin is an active metabolite of oxybutynin that is thought to be responsible for much of the adverse effects of the drug.

Administration

Oxybutynin is available as an oral, transdermal, or topical agent.

COMPREHENSION QUESTIONS

55.1 The most frequent adverse effect seen with anticholinergic drugs used to treat urge incontinence is

A. Anxiety
B. Dry mouth
C. Sweating
D. Elevated blood pressure

55.2 A female patient complains of urinary leakage when she coughs or sneezes. This has not improved after 2 months of pelvic floor training including Kegel exercises, and a trial of tolterodine. Her blood pressure is 160/100 mm Hg. Which of the following would be optimal to add on to her therapy?

A. Oxybutynin
B. Pseudoephedrine
C. Amytriptyline
D. Desmopressin

ANSWERS

55.1 **B.** Common side effects of antimuscarinic drugs are dry mouth, blurred vision, fatique, and dizziness. Antimuscarinic drugs also reduce sweating; this increases the risk of overheating and heat stroke.

55.2 **C.** Pharmacologic treatment of stress incontinence includes sympathomimetics such as pseudoepedrine, which would be contraindicated here because of the hypertension. A combination of a tricyclic like amitriptyline and an anticholinergic appears to provide a synergistic effect that can work in refractory cases.

PHARMACOLOGY PEARLS

- Assessing the type of urinary incontinence is critical to select the correct course of treatment.
- Use of anticholinergics have modest but important benefits to the quality of life, but discontinuation of drugs is high.

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CASE 56

A 35-year-old woman without any past medical history presents to your office with concerns about her weight. Her current BMI is an all-time high of 32 kg/m^2, despite years of dieting and exercise in which she loses weight, and then regains it. Both of her parents are obese and have type 2 diabetes. Her family history is significant also for obesity and multiple obesity-associated complications such as osteoarthritis, type 2 diabetes, obstructive sleep apnea, and coronary artery disease. The patient is very concerned about health implications of her weight. Her mother told her that 25 years ago she was treated with a medication for obesity, and the patient wonders if this would help her.

- How would this patient be classified in terms of obesity and what comorbidities is she now at risk for?
- Based on evidence-based guidelines, what treatment options should be offered to this patient?
- What are the main precautions with pharmacological antiobesity medications?

ANSWERS TO CASE 56

Obesity Diagnosis and Management Options

Summary: An obese 35-year-old woman with a strong family history of obesity-related health complications and a BMI of 32 inquires about pharmacological treatment for her weight.

- The patient's BMI of 32 places her in the category of Class I obesity. Patients who are obese are at risk of morbidity from associated conditions such as (but not limited to) hypertension, dyslipidemia, type 2 diabetes, coronary heart disease, stroke, gallbladder disease, osteoarthritis, sleep apnea and respiratory problems, and endometrial, breast, prostate, and colon cancers. Higher body weights are also associated with increases in all-cause mortality, psychiatric illnesses, asthma, and various somatic dysfunctions.
- Lifestyle modifications to include dietary changes and physical activity have consistently shown to be effective for weight loss. Regardless of the diet or exercise regimen, trials have shown that those that are successful long term are those patients who continue the regimen. Antiobesity medications can be offered in conjunction with lifestyle changes in patients with BMI ≥30 or ≥27 with established health complications of obesity. Currently, only orlistat is FDA approved for obesity treatment and trials show an average of 6- to 9-pound weight loss over 2–4 years. Phentermine is a sympathomimetic that is FDA approved only for short-term obesity management. Its effectiveness is variable based on the literature as many trials have many confounding variables.
- Orlistat has been associated with side effects such as bloating, flatulence, and oily/fatty stools. Phentermine may cause tachycardia, elevations in blood pressure, and psychomotor agitation, and have a high abuse/dependency potential. Other agents that are used for weight loss are not FDA approved.

CLINICAL CORRELATION

The obesity epidemic is exploding worldwide, especially in western societies. According to the American Heart Association, in 2012, 60–80 percent of US adults were either overweight (BMI ≥25) or obese (BMI ≥30). Obesity is further classified as category I (BMI 30–34.9), category II (BMI 35–39.9), and extreme (BMI ≥40). Perhaps more alarming, over 30 percent of US children are now either overweight or obese and over 15 percent are obese, predicting serious adulthood morbidity and mortality. These numbers have increased fivefold in the last 25 years. Obesity is second only to smoking as a cause of preventable death in the United States.

Obesity contributes to morbidity and mortality through its effects on diabetes, hypertension, hyperlipidemia, atherosclerosis, stroke, sleep apnea, cancer, arthritis, and depression. According to the National Cholesterol Education Program, the metabolic syndrome is defined as a constellation of symptoms that include any 3 of the following: **abdominal obesity** (waist circumference ≥40 inches in men or ≥35 inches in women), **elevated triglycerides** (≥150 mg/dL, or treatment for elevated

triglycerides), **low HDL** (<40 mg/dL in men or <50 mg/dL in women or treatment for low HDL), **elevated BP** (≥130/85 mm Hg or treatment for hypertension), and **elevated fasting glucose** (≥100 mg/dL or glucose lowering treatment). Although metabolic syndrome is a serious cause of illness, treatment consists of management of each individual component and aggressive screening for other components. When obesity is associated with metabolic syndrome or other risk factors, it requires aggressive intervention.

APPROACH TO: Antiobesity Drugs

OBJECTIVES

1. Know the classes of antiobesity medications and their mechanisms of action.
2. Know the indications for use of these drugs.
3. Know the adverse effects of antiobesity agents.

DEFINITIONS

Body mass index: BMI is defined as mass in kilograms divided by the square of height in meters.

Metabolic syndrome: The co-occurrence of several clinical findings, including diabetes, obesity, and cardiovascular disorders.

Overweight: BMI 25–29.9

- Class I Obesity: BMI 30–34.9
- Class II Obesity: BMI 35–39.9
- Class III Obesity (Extreme Obesity): BMI ≥40

Sympathomimetic: An agent that produces effects similar to those observed upon physiologic activation of the sympathetic nervous system.

DISCUSSION

Class

Treatments for obesity include dietary changes, exercise programs, behavioral modifications, surgery, and medications. Despite this wide array of potential treatments, long-term outcomes are abysmal. Most experts agree that a truly successful strategy involves a combination of diet, exercise, and behavioral changes, with or without surgery and medications. Many diets have been promoted and studies show that all have similar effectiveness in the long term. Restricted calorie diets in overweight or obese individuals generally promote 8 percent weight loss per year. The most successful diets include support groups that incorporate behavioral modifications.

Exercise can also promote weight loss; however, exercise alone is rarely adequate. Exercise added to dietary change is more successful, as exercise prevents the slowing of metabolism from caloric deficit. Behavioral modifications emphasize portion control, emotions associated with eating, and adherence to dietary plans. During the intervention period they usually produce up to 10 percent weight loss; however, weight is often regained after the program ends.

Surgical treatments of obesity have the single greatest efficacy, but also pose the greatest risk. Surgical procedures can reduce body weight by 35 to 40 percent with maintenance for 15 years. Surgery is indicated in patients with a BMI over 40, or in patients with a BMI of 35 with significant comorbidity. Success is higher with surgery in patients who are committed to lifestyle changes (diet/exercise/portion control/appropriate food choices) and those who have ongoing support mechanisms and psychological support. Risks of surgery include prolonged postoperative recovery, infection, electrolyte derangements, dehydration, excess skin, nutritional deficiencies, dumping syndrome, deep vein thrombosis, and cholecystitis. Perioperative mortality can reach 1 percent and is reduced when medical and psychiatric conditions are controlled preoperatively. Even when surgery is completely successful without complications, patients can be expected to have malabsorption issues requiring supplementation with calcium, thiamin, iron, and vitamin B_{12}. In addition, many medications will have altered pharmacokinetics following successful surgery. The surgery results in reduced surface area for absorption and will significantly reduce absorption of extended-release drugs. Absorption of medications that are pH sensitive will be altered by the alkaline environment.

Antiobesity medications generally produce 5 to 10 percent weight loss. Drug therapy is indicated if the patient has a BMI ≥30, or a BMI ≥27 with metabolic syndrome or significant obesity complications. There are three classes of drugs: a **lipase inhibitor,** the **sympathomimetics** and **selective serotonin receptor agonists** (Table 56–1). **Orlistat** is the only lipase inhibitor currently produced and, unlike all other antiobesity medications, is approved for long-term treatment of obesity. It is available in both prescription and over-the-counter forms and is dosed three times a day with meals. The over-the-counter formulation is a 50 percent reduced dose of the prescription strength medication. Orlistat is not systemically absorbed, and side effects are concentrated on the gastrointestinal tract. Most common adverse events include flatulence, greasy/loose stools, and abdominal pain. In addition, fat-soluble vitamins may not be absorbed.

Sympathomimetics act centrally to suppress appetite. They are approved only for short-term treatment of obesity and are typically administered once daily. **Phentermine** is the most commonly prescribed sympathomimetic and has been available since the 1970s. A recently approved weight-loss drug combines **phentermine** with the antiepilepsy drug, **topiramate**. All of the sympathomimetics can produce hypertension, tachycardia, insomnia, and other symptoms of sympathetic activation. The sympathomimetic, **sibutramine,** was removed from the US market in 2010 due to concerns related to cardiovascular side effects. These drugs also have the potential for addiction, and hence are classified by the DEA as scheduled substances.

Food intake can be reduced by serotonin; therefore, serotonin receptors have long been targeted for the development of weight-loss drugs. Nonselective serotonin agonists, such as fenfluramine and dexfenfluramine, are effective in weight

Table 56–1 • PHARMACOLOGICAL AGENTS IN OBESITY MANAGEMENT

Class	Drugs	MOA	Side Effects
Lipase Inhibitor	Orlistat	Inhibits fat breakdown and absorption within the gut	Flatulence Abdominal cramping Loose stools Malabsorption of fat-soluble vitamins
Sympathomimetic	Phenteramine Benzphetamine Diethylpropion Phendimetrazine Methamphetamine	Anorexiants; methamphetamine is also a stimulant	Drug Abuse Tachycardia/palpitations Hypertension Insomnia
Selective Serotonin Receptor Agonist	Lorcaserin	Anorexiant	Elevated blood pressure
Combination Drugs	Phentermine/ topiramate	Anorexiant; anticonvulsant	Elevated heart rate Constipation
Antidepressant	Buproprion	Inhibits dopamine and norepinephrine transport; active metabolites are amphetamine-like	Anxiety Insomnia Seizures
Antiseizure	Topiramate	Wide range antiseizure activity including prolonging Na^+ channel inactivation and promoting $GABA_A$ activity	Fatigue Cognitive impairment Peripheral neuropathy
Biguanide	Metformin	Decreased hepatic glucose production Enhances insulin action Decreased intestinal glucose absorption	Lactic acidosis (esp. in renal impairment and after IV contrast) Diarrhea Nausea Abdominal pain
Incretin analog	Exenatide	Promotes insulin release through activation of GLP-1 receptors on pancreatic β cells	Nausea Hypoglycemia Anti-exenatide antibodies Decreased absorption of other drugs

loss; however, these drugs increase the risk of serotonin-associated valvular heart disease, likely through actions at the serotonin 2B receptor and hence were taken off the US market by the FDA. Lorcaserin, which is a selective serotonin 2C receptor agonist, has recently been approved by the FDA.

Although many medications can cause weight gain, a few promote weight loss, and these are sometimes used **off label** for this purpose (Table 56–2). **Bupropion** inhibits dopamine and norepinephrine uptake. Unlike other antidepressants, it can cause weight loss. Seizures are a potential serious side effect of bupropion. **Topiramate** is an antiepileptic drug that is also indicated for migraine prophylaxis. It inhibits neuronal firing and synaptic transmission. Side effects that limit its use include induction of cognitive deficits and peripheral neuropathy. Clinical trials support the

Table 56–2 • TREATMENT APPROACH TO OVERWEIGHT/OBESE PATIENTS

BMI	Obesity Class	Advise Diet	Advise Exercise	Offer Medication[#]	Offer Surgery Consultation
<18.5	Underweight	Yes[*]	Yes[*]	No	no
18.6-24.9	Normal	Yes	Yes	No	No
25-29.9	Overweight	Yes	Yes	If comorbidities	No
30-34.9	Obesity I	Yes	Yes	Yes	no
35-39.9	Obesity II	Yes	Yes	Yes	If comorbidities
≥40	Obesity III Extreme obesity	Yes	Yes	Yes	Yes

[*]In underweight patients, one should perform a thorough history, examination, review of systems, and consider various differentials for the etiology. A modification of dietary intake and physical activity needs to be considered to appropriately optimize the net caloric goals to attain appropriate BMI. Hence, avoidance of overexpenditure, avoidance of drugs/herbs/supplements that promote weight loss, and optimizing caloric intake would be ideal if other organic causes have been ruled out.

[#]Medications are not first line in obesity management. However, trials have shown that in addition to diet and exercise they are more effective than any modality alone. Especially in patients who have not been successful with lifestyle changes and have comorbid conditions, medications can be offered.

use of a phentermine/topiramate combination specifically for treatment of obesity; this therapy awaits FDA approval.

Two medications used to treat diabetes also produce weight loss. This is an **off-label** use of these drugs. **Metformin** is a biguanide that exhibits insulin-dependent and insulin-independent effects. Metformin enhances insulin sensitivity. Independent of insulin effects, metformin inhibits hepatic glucose output and increases glucose uptake by peripheral tissues. A life-threatening complication from metformin is lactic acidosis, which is most prevalent in elderly patients with renal insufficiency or with IV contrast administration. Nausea and diarrhea are the most common side effects of metformin. Metformin is contraindicated in renal or hepatic impairment. **Exenatide** is an incretin analog that promotes insulin release from pancreatic β cells in the presence of glucose. It is a peptide that must be given by daily subcutaneous injection. Its use can be limited by the formation of antibodies against exenatide. It also causes nausea, hypoglycemia, and decreased absorption of other drugs.

Mechanism of Action

Orlistat inhibits gastric and pancreatic lipases and blocks the breakdown and absorption of fat. Prescription strength reduces dietary fat absorption by up to 30 percent; over–the-counter preparations reduce fat absorption by up to 25 percent. Orlistat is not absorbed systemically.

Sympathomimetics increase the release of norepinephrine and dopamine from presynaptic neurons. They stimulate the hypothalamus to decrease appetite through effects on the satiety center. The combination drug containing phentermine/topiramate combines the sympathomimetic action of phentermine with the anticonvulsant activity of topiramate. Topiramate acts centrally to inhibit voltage-gated sodium channels, inhibit excitatory pathways, and enhance GABAergic neurotransmission.

Serotonin receptor agonists are known to promote weight loss, although nonselective forms carry significant risks of cardiovascular side effects, most likely due to actions on the serotonin 2B receptor. The newly approved drug, lorcaserin, is a selective serotonin agonist that specifically targets the serotonin 2C receptor, which is thought to prevent the adverse cardiovascular effects. Side effects include increased blood pressure.

Pharmacokinetics

Orlistat is not absorbed. Its two inactive metabolites are produced by breakdown within the GI tract, and excreted in the feces.

Sympathomimetics are easily absorbed; peak plasma levels are attained within 2 hours of ingestion. First-pass metabolism is typically extensive. **Phentermine** is not metabolized, and is excreted by the kidneys. Both extended-release and immediate-release formulations are available. **Benzphetamine** is excreted in urine following metabolism to methamphetamine and amphetamine, as well as inactive para-hydroxylated derivatives. **Diethylproprion** has active metabolites, produced by *N*-dealkylation and reduction in the liver, with longer half-lives than the parent compound. It is excreted by the kidneys. Like phentermine, **phendimetrazine** is available in both immediate- and extended-release formulations. It is metabolized by the liver and excreted by the kidneys. **Methamphetamine** is metabolized by the liver into amphetamine and inactive compounds. It is excreted by the kidneys.

COMPREHENSION QUESTIONS

56.1 A 32-year-old woman with obstructive sleep apnea, chronic kidney disease hypertension, and type 2 diabetes with peripheral neuropathy being managed with appropriate medications seeks your advice for pharmacological intervention to promote weight loss. Currently, her height is stable at 62 inches, but her weight is at 180 pounds (BMI of 32). Although improved from a BMI of 34 with intensive lifestyle changes, in the last 6 months her weight has reached a plateau. Today her BP is 170/102 and her hemoglobin A1c is 8.8 percent. Based on her BMI, comorbidities, and patient preference you decide to prescribe a weight loss drug. Which of the following would be least likely to exacerbate her chronic conditions?

A. Phentermine
B. Phentermine/topiramate
C. Lorcaserin
D. Orlistat
E. Topiramate

56.2 A 50-year-old man with a BMI of 45 has tried over-the-counter orlistat with some success. He is motivated to lose weight and has joined a gym. You choose to start pharmacotherapy with phentermine. What is the mechanism of action of this drug?

A. Appetite suppression
B. Inhibition of GABA neurotransmission
C. Inhibition of gastric lipase
D. An incretin analog
E. Inhibition of dopamine reuptake

56.3 Forty-eight hours after starting orlistat, a patient calls your office complaining of severe abdominal cramping and loose/greasy stools. He has just eaten a bag of reduced fat potato chips. He also takes metformin, which has controlled his type 2 diabetes for several years. You advise him the following:

A. Stop orlistat immediately, and list this as a drug allergy.
B. Increase the dose of orlistat.
C. Increase dietary fat to make up for the fat lost in the stools.
D. This is an expected side effect of orlistat. Further reduction in fat consumption will alleviate these symptoms.
E. Stop metformin.

ANSWERS

56.1 **D.** With the patient's BMI that is still in Obesity Stage 1 despite intensive lifestyle changes along with multiple medical comorbidities, it would be appropriate to offer a trial of a pharmacological agent. The sympathomimetic phentermine or any product containing this medication could worsen the patient's already significantly elevated BP and lead to other cardiovascular complications. Although lorcaserin is selective for the serotonin 2C receptor, which decreases cardiovascular side effects, increased blood pressure is associated with its use and therefore, it would not be a good choice for this patient. Topiramate has been shown to offer weight loss; however, it may also worsen her existing neuropathy. Orlistat will help the patient decrease her intake of fat and is the best option for this patient.

56.2 **A**. Phentermine acts centrally to inhibit noradrenergic reuptake and suppress appetite. It does not affect dopamine or GABA transmission. Inhibition of GABA transmission is a mechanism of action of topiramate, which can cause weight loss (off label use). Bupropion acts through inhibition of dopamine reuptake; it can also lead to weight loss (off label use). Gastric lipase inhibition is produced by orlistat. Exenatide is an incretin analog and causes weight loss (off label use) by acting centrally on the hypothalamic satiety center.

56.3 **D**. Orlistat inhibits gastric lipase and the breakdown/uptake of fat in the gut. When too much fat is consumed, the patient will have abdominal cramping, diarrhea, and greasy stools. This patient has just consumed potato chips, and even though they were reduced fat, he is experiencing expected side effects that should motivate him to decrease future fat consumption. If he either increases fat consumption or increases his dose of orlistat, he will increase these adverse reactions. Because he is experiencing expected side effects of orlistat, this should not be taken as a drug allergy. Although these side effects can occur with metformin, he has tolerated this drug and needs it for control of his diabetes.

PHARMACOLOGY PEARLS

- Antiobesity medications have a success rate of 5–10 percent weight loss.
- Orlistat is the only antiobesity medication currently approved for long-term use.
- Orlistat works by blocking fat digestion and absorption in the gastrointestinal tract.
- Sympathomimetics cause side effects through sympathetic activation.

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SECTION III

Listing of Cases

Listing by Case Number

Listing by Disorder (Alphabetical)

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Listing by Case Number

Listing by Disorder (Alphabetical)

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