PHARMACOLOGY KNOWLEDGE OBJECTIVES 2022

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Association of Medical School Pharmacology Chairs

1. INTRODUCTION

1.1PREFACE TO THE 2022 EDITION

The Preface to the First Edition is provided below this current preface. It is included to provide some historical perspective on the development and purpose of the Knowledge Objectives. The last iteration of the Knowledge Objectives occurred in 2012. A few sections were updated around 2017, but a full update did not occur. This iteration is the result of an agreement with Association of Medical School Pharmacology Chairs (AMSPC) and ASPET's Division for Pharmacology Education (DPE). Both groups realize the value of such a document to provide consistency to the pharmacology education of our future healthcare providers. Members of both organizations have worked together to update this document and make it available to all who need the guidance it contains. The Editors thank the Section Chairs and the members of each Committee for their hard work and dedication to creating this update.

Several important points need to be made to help facilitate the purpose of this document.

1. This document is intentioned to be used by faculty as a guide, or recommendation, for faculty to use to develop content for presentations, lectures, self-study modules, small-group activities, etc., for students.
2. It is not a compendium of information, but rather suggestions of the content to be presented, suggestions from pharmacologists who have expertise and experience in each field or section.
3. There will be some redundancy of content in various topics. Each faculty member should decide for themselves what to use, and how to use the information suggested for each topic to best suit the goals of their curriculum.
4. The drugs noted in the document show major, prototypical drugs in CAPS. Other drugs that may be important in an area, but are not major and/or prototypical, are in lowercase. The drug lists are NOT all inclusive, nor should they be. There may be an appendix developed with a more comprehensive list of drugs in each topic section. However, the Knowledge Objectives should be succinct and confine drugs listed to only the minimum drugs that are exemplary for a topic being addressed.
5. There is a suggested curricular time for each topic area. This is to provide some guidance as to the importance of each topic. However, with the wide variability of curricula today, these may be hard to align with any given academic program. Yet, this information is the best estimate from the body of experts who have updated the Knowledge Objectives.

In summary, this document is intended for use by experienced faculty, junior faculty, or new faculty, and faculty who may be charged with presentations in areas of pharmacology they have not presented before. It is NOT intended as a study guide for students, or as a comprehensive compendium of information students should have to move into their clinical training. Faculty may share this information with students if they so choose, but hopefully with the above caveat. If anyone notes a discrepancy or error in this document, the editors would appreciate being notified of such an instance. As with all knowledge, this should be considered a 'work in progress' that needs updating periodically, especially considering the dynamic nature of the discipline of pharmacology.

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1.2 PREFACE TO THE FIRST EDITION

It is the purpose of this document to identify the minimum essential knowledge in pharmacology which every medical student trained as an undifferentiated physician must have at the time of graduation from medical school. These knowledge objectives were developed by a committee of the Association of Medical School Pharmacology Chairs (AMSP) charged with developing an essential knowledge base in pharmacology for medical students. This document is intended to assist faculty members in medical schools in the United States in organizing their pharmacology curricula. Each topic was generated by a special subcommittee of the Association of Medical School Pharmacology chairmen with expertise in a particular area of pharmacology. The objectives were not designed for any particular medical pharmacology course, but instead are meant to serve as guidelines for the minimum knowledge of pharmacology that medical students should possess when they graduate from medical school.

Even though the essential knowledge objectives included in this document have been oriented toward the second-year medical pharmacology course, curricula may differ in some schools where these principles and objectives are covered in other years of the medical school curriculum.

An attempt has been made to define the essential learning or knowledge objectives and the minimum number of drugs which should be taught. Whenever possible prototypical or model drugs are included with major emphasis on teaching the principles of pharmacology. Drugs in current use will usually be used in each organizing element. However, in certain instances drugs which are not currently used in therapeutics or drugs which may be used as pharmacological tools may be included if they better demonstrate a principle or special pharmacologic mechanism. Thus, the reasons for including a drug are: 1) extent of therapeutic use by being listed in the 200 most commonly prescribed drugs in the United States (e.g. *National Prescription Audit); or 2) its recommendation by one of the expert committees listed at the beginning of each section based on its demonstrating a principle of drug action or being of historical interest. The drugs listed as PRIMARY drugs (ALL CAPITALS) in the index are considered by the above criteria to be the most important drugs and are strongly recommended to be taught in every medical pharmacology course. Some selected SECONDARY drugs (small letters) are also included in the index which are considered less important but should be taught if time permits.

The principles and knowledge objectives included in this document will usually center around mechanisms of action, actions on organ systems, pharmacokinetics, therapeutic indications including some disease entities, adverse effects, contraindications and drug interactions. Every effort has been made to reduce the number of drugs being taught in medical schools today and focus on the essence of pharmacology emphasizing principles and knowledge objectives. Some areas of pharmacology and some drug classes such as diagnostic agents, special nutritional materials and some agents with a limited specific use are not covered in this document. These materials are best learned at the time of exposure to a particular clinical specialty.

The results of surveys of medical school pharmacology departments carried out in 1983 by P.N. Bogner and M.D. Alschuler at the University of Illinois; for the Association of Medical School Pharmacology (AMSP) carried out by Ted Brody at Michigan State University (1984-85); and by a questionnaire under the combined auspices of the ASPET Educational Affairs subcommittee on medical education and AMSP were used as guides in determining the total number of contact hours for a medical pharmacology course and the number of hours devoted to each topic area. We hope this document will provide guidance for medical school pharmacology departments as well as clinical departments in pharmacology and will better prepare physicians in pharmacology, therapeutics and toxicology for the practice of medicine on a scientific basis.

*conducted by IMS America, Ltd., Ambler, Pa.

1.3 Table of Contents

2. GENERAL PRINCIPLES

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General Principles of Pharmacology

Basic Principles of Pharmacology			
2.1 Introduction			
Recommended Curriculum Equivalent: 7.0 hr.			
2.1.1 Terminology			
Definitions and Terms		Relationship to Other Disciplines-describe the relationship of pharmacology to other disciplines	
Pharmacology Drugs Receptors Targets	Agonists Antagonists	Anatomy Biochemistry Microbiology Physiology	Chemistry Physics Toxicology
2.1.2 Content Recommendations			

2.1.2.1 Definitions and Terminology

1. Define pharmacology, explaining its role in understanding therapeutics.
2. Explain the relationship of pharmacology as a biomedical science with other biomedical sciences and how they are mutually supportive.
3. Define foundational terms: drugs, drug targets, receptors, agonist, antagonist. Note that some drugs act via non-receptor mechanisms: antacids, metal complexing agents; osmotic diuretics, etc

2.1.2.2 Physiology and pathophysiology

1. Describe the families of receptors involved in normal physiological function; e.g., ion channels; G protein-coupled receptors (GPCR); kinases; nuclear receptors
2. Describe second messenger systems that link receptors to physiological cellular activity.
3. Explain how drugs interact with receptors and second messenger pathways to induce changes in physiological function.

2.1.2.3 Pharmacokinetics

1. Define pharmacokinetics, explaining how this information links to therapeutic uses of drugs.
2. Describe the mechanisms involved in the major processes of pharmacokinetics, absorption, distribution, metabolism, elimination, and excretion.
3. Describe time-action relationships and their importance to therapeutic use of drugs in clinical medicine.
4. Explain the importance of chemical aspects of drug structure, including pKa, polarity, acid/ base characteristics, solubility, partition coefficients, and how they affect the processes of pharmacokinetics of

small molecule drugs. Differentiate biologics from small molecule drugs, and indicate commonly occurring differences in their pharmacokinetic properties.

5. Describe the mechanisms of drug movement across membranes and the importance of these processes to drug absorption, distribution, elimination, and excretion.
6. Describe the effects of body compartments and barriers on drug distribution.
7. Explain the relationship of lipid solubility, tissue blood flow, route of administration, pH, and other factors that may alter absorption.
8. Define important concepts of pharmacokinetics such as half-life, apparent volume of distribution, area under the curve, bioavailability, first-pass metabolism, and clearance. Relate them to steady state, plateau principles, time to steady state, loading doses, and other concepts.
9. Explain first-order, mixed, and zero-order kinetics, relating the processes to drug clearance, half-life, and other relevant concepts. Define what is meant by linear pharmacokinetics.
10. Be able to estimate clearance, elimination half-life, and apparent volume of distribution, from concentration versus time data following intravenous drug administration.
11. Distinguish between renal and nonrenal clearance of drugs and how to determine their contributions to total drug clearance.
12. Explain how protein binding, drug sequestration, lymphatics, and tissue perfusion affects drug pharmacokinetics.
13. Describe Phase 1 and Phase 2 metabolism of drugs, explaining the role of cytochrome P450 enzymes and other enzyme isoforms in drug metabolism, including enzyme induction and inhibition.
14. Describe how age, sex, and disease may alter pharmacokinetic processes.
15. Contrast the concepts of termination of drug effect, drug elimination, and drug excretion.
16. Explain the major sites of drug excretion, and the special sites for specific drug classes.

2.1.2.4 Pharmacodynamics

1. Define pharmacodynamics, explaining how this information links to therapeutic uses of drugs.
2. List the major families of drug targets and the types of molecular interactions between drugs and their targets. Distinguish between selectivity and specificity with reference to drug-target binding and explain their relevance to adverse effects of drugs.
3. Explain the difference between drug potency and drug efficacy.
4. For drugs whose targets are physiological receptors, define what is meant by spare receptors and their functional significance for drug action, signal transduction cascades,
5. Define dose-response and log-dose-response relationships, graded and quantal; explain their use to provide information about potency, efficacy, and safety predictability.

6. Define agonists (full, partial, and inverse) relating affinity and efficacy to these concepts, and antagonists (competitive, reversible, noncompetitive and irreversible) and the resultant consequences for their use.

7. Describe the use of quantal dose-response relationships and calculation of safety indices and the use of such indices in clinical decisions.

8. Explain structure-activity relationships for small molecules as a mechanism for modeling receptors, their active sites, and drug development.

9. Describe receptor regulation, de-sensitization and super-sensitivity, explaining the mechanisms of down-regulation and up-regulation of receptors.

2.1.2.5 Pharmacogenetics/Pharmacogenomics

1. Define pharmacogenetics and pharmacogenomics and explain their clinical relevance.
2. Describe genetic polymorphisms, including single nucleotide polymorphisms, gene deletions, amplifications, and duplications, and their effect on protein structure, configuration, and/or concentration, relating to clinical relevance.

3. Identify the major genetic polymorphisms that affect drug metabolism and disposition; drug toxicity and drug responses, indicating their clinical relevance; including polymorphisms in Phase 1 enzymes (such as CYP2D6, CYP2C9, CYP2C19; pseudocholinesterase), Phase 2 enzymes (e.g., NAT2, TPMT); drug transporters; and in drug receptor (including GPCRs) and effector systems.

4. Describe monogenic pharmacogenetic traits that are known, including their clinical relevance.

2.1.2.6 Drug Interactions

1. Explain the mechanisms and clinical relevance of interactions of drugs with other drugs, nutrients, herbal products, recreational drugs, and other potential substances.
2. Explain the importance of knowledge of a complete patient drug history in minimizing negative interactions with drugs and other agents commonly taken by patients.
3. Describe the types of drug interactions, including pharmacokinetic, pharmacodynamic, toxicological, etc., providing examples of each. Explain the types of outcomes, including additivity, synergy, potentiation, antagonism, and how some interactions may be therapeutically beneficial.

2.1.2.7 Drug Development, Evaluation, and Regulation

1. Describe the process of drug development including pre-clinical studies, clinical studies, and the role of regulatory agencies in this process. Note differences between generic and brand name (proprietary) drugs, how these are evaluated by FDA, and what that really means. Note the increasing importance of biologics, and biosimilars (the generic equivalent of biologics).
2. Describe and define placebo and placebo effect and how they are used in drug development, Institutional Review Boards, and the importance of safety in drug testing.
3. Describe and explain the phases of drug trials as defined and regulated by various agencies such as the FDA and DEA, including any post marketing phases.
4. Identify recognized and accepted sources of drug information, such as textbooks, websites, etc.

2.2 Principles of Therapeutics

Recommended Curriculum Equivalent: 1.0 hr.

2.2.1 Pharmacology Topics

Pharmacokinetics	**Pharmacodynamics**
Absorption	Mechanisms of Drug Action
Distribution	Structure-Activity Relationships
Metabolism	Concentration and Dose Effect Relationships
Elimination	Types of Agonists and Antagonists
Excretion	Mechanisms of Drug Adverse Effects
Clearance	Mechanisms of Drug Interactions
Area Under the Curve	Signal Transduction
Half-Life	Cell Cycle and its Regulation
Routes of Administration	

2.2.2 Content Recommendations

2.2.2.1 Physiology and pathophysiology

1. Describe factors that make each patient unique in terms of response to drugs.

2.2.2.2 Pharmacodynamics

1. Explain the importance of understanding a drug's mechanism(s) of action (MOA) for its use as a therapeutic agent.

2. Explain the importance of the MOA's role in predicting and understanding adverse effects and drug interactions.

3. Describe the importance of understanding the use and interpretation of quantal versus graded dose-response relationships.

2.2.2.3 Pharmacokinetics

1. Describe the various processes that govern absorption, distribution, metabolism, elimination and excretion of drugs.

2 Explain the importance of understanding various pharmacokinetic parameters including area under the curve, half-life, clearance, routes of administration, apparent volume of distribution, and protein binding, as they apply to the use of drugs as therapeutic agents.

2.2.2.4 Pharmacogenetics and Pharmacogenomics

1. Define pharmacogenetics and pharmacogenomics.
2. Describe the types of genetic polymorphisms and their potential effects on drug responses in individuals.

3. AUTONOMIC PHARMACOLOGY

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Autonomic Pharmacology

3.1 Introduction and History

Recommended Curriculum Equivalent: 1.0hr.

3.1.1 Neuronal Drugs

Amphetamine	Metyrosine (Historic)
Botulinum Toxin	Phenelzine (Historic)
Carbidopa	Reserpine (Historic)
Cocaine	Muscarine (Historic)
Entacapone	
Physostigmine	
Tetrabenazine	

3.1.2 Content Recommendations

3.1.2.1 Physiology and pathophysiology

1. Specify the anatomical projections of the sympathetic and parasympathetic autonomic nervous system (ANS).
2. Explain the biosynthesis of autonomic neurotransmitters.
3. Identify the location of cholinergic and adrenergic receptors and their subtypes.
4. Describe the responses to activation of cholinergic and adrenergic receptors.
5. Describe the evidence for the development of the concept of neurotransmitters, co-transmitters, and end-organ specificity.
6. Describe homeostasis, fight-or-flight, and rest-and-digest regarding the ANS.
7. Classify the responses of end organs to activation and inhibition of each division of the ANS.
8. Compare the two major cholinesterases: acetylcholinesterase (AChE) and butyrylcholinesterase (BuChE) as to anatomical locations, sites of synthesis, and function.
9. Relate the concept of dominant tone to transmitter release and regulation.
10. Describe the role of both muscarinic and nicotinic receptors in the autonomic ganglia.
11. Explain the rationale for the historically used drugs in ANS-related diseases.

3.1.2.2 Pharmacodynamics

1. Identify drugs that inhibit the metabolism of acetylcholine and norepinephrine.
2. Predict the effect of catechol-O-methyltransferase peripheral inhibition.
3. Identify drugs that inhibit catecholamine synthesis.
4. Identify drugs that block storage vesicle transport systems.
5. Identify drugs that inhibit the release of acetylcholine.
6. Predict the mechanism by which drugs facilitate the release of norepinephrine.
7. Describe the mechanism by which drugs inhibit the reuptake of norepinephrine into the adrenergic neuron.

Autonomic pharmacology

3.2 Cholinergic and Nicotinic Agonists

Recommended Curriculum Equivalent: 3.0 hr.

3.2.1 Drug Classes and Drugs

Direct Acting Cholinergic Agonists		Indirect Acting Cholinergic Agonists	
Muscarinic	**Nicotinic**	**Cholinesterases inhibitors**	**Related Drugs**
Acetylcholine Bethanechol Pilocarpine	Nicotine Varenicline	Pyridostigmine Neostigmine Physostigmine Parathion (pesticide)	Pralidoxime Sarin

3.2.2 Content Recommendations

3.2.2.1 Physiology and pathophysiology

1. Describe synthesis, storage, release, and inactivation of cholinergic agonists.
2. List the steps in the synthesis, storage, release, and inactivation of acetylcholine and drugs that interface with those processes.
3. Explain why anticholinesterases are classified as reversible or irreversible.

3.2.2.2 Pharmacodynamics

1. Explain the mechanism of actions, including second messenger systems, if applicable, of drugs activating muscarinic and nicotinic receptors.
2. Explain the chemical makeup of the active site of AChE (anionic and esteratic) as to attraction, attachment, and rates of the breakdown of various substrates and inhibitors.
3. Distinguish the mechanism by which pralidoxime reactivates phosphorylated AChE.

3.2.2.3 Pharmacokinetics

1. Summarize the variations in the pharmacokinetics of muscarinic and nicotinic agonists
2. Relate the duration of action of anticholinesterases with sites and type of attachment to the enzyme.

3.2.2.4 Adverse effects, drug interactions, and contraindications

1. Predict and summarize the rationale for the major adverse effects of cholinergic agonists.
2. List and describe the rationale for contraindications of cholinergic drugs.

3.2.2.5 Therapeutic uses

1. List the therapeutic uses of cholinergic agonists.
2. Explain why nicotine is not used clinically (except as a smoking deterrent).

Autonomic pharmacology

3.3 Cholinergic Antagonists

Recommended Curriculum Equivalent: 2.0 hr.

3.3.1 Drug Classes and Drugs

Muscarinic Receptors Antagonists	Nicotinic Receptors Antagonists		
Atropine Ipratropium Scopolamine Tolterodine Oxybutynin Darifenacin Dicyclomine Glycopyrrolate Solifenacin Tiotropium Tropicamide	Neuromuscular Junction	Drugs Acting on Autonomic Ganglia	Related Drugs
	Cisatracurium Rocuronium Succinylcholine Vecuronium Tubocurarine (Historic)	Mecamylamine	Sugammadex (reversal agent)

3.3.2 Content Recommendations

3.3.2.1 Physiology and pathophysiology

1. Revisit section 3.1.2.1.
2. Predict and specify the different nicotinic receptor subtypes, including their subunit composition, receptor location, and function.

3.3.2.2 Pharmacodynamics

1. Identify and specify muscarinic and nicotinic antagonist properties.
2. Contrast and compare the competitive and noncompetitive (depolarizing and nondepolarizing) neuromuscular junction blocking drugs.

3.3.2.3 Pharmacokinetics

1. Summarize the major variations in the pharmacokinetics of muscarinic and nicotinic antagonists. (As crossing the blood-brain barrier and metabolism)

3.3.2.4 Adverse effects, drug interactions, and contraindications

1. Predict and specify the rationale for the major adverse effects of muscarinic and nicotinic antagonists.
2. Predict and specify the rationale for the major adverse effects and their relevance to the two classes of neuromuscular blocking drugs.
3. Predict the major adverse effects of drugs acting on autonomic ganglia.
4. Predict and specify the rationale for the major contraindications of muscarinic and nicotinic antagonists.

3.3.2.5 Therapeutic uses

1. Explain the rationale for the therapeutic uses of muscarinic antagonists.
2. Explain the differential uses of nondepolarizing versus depolarizing neuromuscular blocking drugs and their limitations.

Autonomic Pharmacology		
3.4. Adrenergic Agonists		
Recommended Curriculum Equivalent: 3.5 hr.		
3.4.1. Drug Classes and Drugs		
Nonselective Adrenergic Agonists	**Selective Alpha Adrenergic Agonists**	
Dopamine Epinephrine Norepinephrine	Phenylephrine (alpha 1) Brimonidine (alpha 2) Clonidine (alpha 2) Methyldopa (alpha 2)	
Nonselective Alpha-Adrenergic Agonists	**Nonselective Beta-Adrenergic Agonists**	**Selective Beta-Adrenergic Agonists**
Oxymetazoline	Isoprotereno l	Dobutamine (beta 1) Albuterol (beta 2)
Indirect Acting Agents	**Mixed Acting Agents**	
Cocaine Amphetamine Tyramine (dietary component)	Pseudoephedrine Ephedrine	
3.4.2 Content Recommendations		
3.4.2.1 Physiology and pathophysiology 1. Revisit section 3.1.2.1 2. Describe receptor selectivity of norepinephrine and epinephrine. 3. Describe the differences between direct and indirect-acting and mixed adrenergic drugs.		
3.4.2.2 Pharmacodynamics 1. Explain the mechanism of actions, including the second messenger systems of drugs activating adrenergic receptors. 2. Compare and contrast the pharmacology of selective and nonselective adrenergic agonists.		
3.4.2.3 Pharmacokinetics 1. Relate the pharmacokinetic principles of selective and nonselective adrenergic agonists to their administration for therapeutic use.		
3.4.2.4 Adverse effects, drug interactions, and contraindications 1. List the major adverse effects of selective and nonselective adrenergic agonists. 2. Explain major drug interactions and the contraindications for selective and nonselective adrenergic agonists.		
3.4.2.5 Therapeutic uses 1. Explain the major therapeutic uses of selective and nonselective adrenergic agonists.		

Autonomic Pharmacology		
3.5 Adrenergic Antagonists		
Recommended Curriculum Equivalent: 1.5 hr.		
3.5.1 Drug Classes and Drugs		
Nonselective Beta-Adrenergic Antagonists	**Selective Beta-Adrenergic Antagonists**	
Propranolol Timolol	Metoprolol Atenolol Nebivolol Esmolol	
Nonselective Alpha Adrenergic Antagonists	**Selective Alpha 1 Adrenergic Antagonists**	**Mixed Alpha and Beta Adrenergic Antagonists**

Phenoxybenzamine Phentolamine	Prazosin Tamsulosin Terazosin	Carvedilol Labetalol

3.5.2 Content Recommendations

3.5.2.1 Physiology and pathophysiology

1. Revisit section 3.1.2.1

3.5.2.2 Pharmacodynamics

1. Compare and contrast the pharmacology of the selective and nonselective adrenergic antagonists.

3.5.2.3 Pharmacokinetics

1. Relate the pharmacokinetic principles of selective and nonselective adrenergic antagonists to their administration for therapeutic use.

3.5.2.4 Adverse effects, drug interactions, and contraindications

1. List the major adverse effects of selective and nonselective adrenergic antagonists.
2. Explain major drug interactions and the contraindications for selective and nonselective adrenergic antagonists.

3.5.2.5 Therapeutic uses

1. Explain the major therapeutic uses of selective and nonselective adrenergic antagonists.

4. DRUGS ACTING ON THE CENTRAL NERVOUS SYSTEM

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4.1 Introduction to Pharmacology of the Central Nervous System
Understanding how drugs affect the central nervous system depends upon an integral knowledge of neuroanatomy, biochemistry, physiology, and basic pharmacological principles. A core medical curriculum in pharmacology of the central nervous system requires at least 21 hours

4.2 Neurotransmitters, Neuromodulators, and Receptors	
Recommended Curriculum Equivalent: 1.5 hr	
4.2.1 Endogenous Agents	
Primary agents	Secondary agents
ACETYLCHOLINE (ACH) DOPAMINE (DA) 5-HYDROXYTRYPTAMINE (5-HT) GAMMA-AMINOBUTYRIC ACID (GABA) GLUTAMATE (GLU) HISTAMINE (Hist) NOREPINEPHRINE (NE)	adenosine (Ad) adenosine triphosphate (ATP) aspartate (Asp) beta-amyloid beta-endorphin bradykinin brain derived neurotrophic factor (BDNF) endorphins epinephrine (Epi) dynorphins enkephalins glycine leptin nerve growth factor (and other growth factors) (NGF) nitric oxide (NO) orexins substance P (SP)

4.2.2 Content Recommendations
4.2.2.1 Physiology and pathophysiology List the major neurotransmitters in the brain, their predominant anatomical pathways, and their associated relevant disorders. Compare and contrast G protein coupled receptors and ligand-gated ion channels and describe the major effector systems coupled to various G-proteins. List the major classes of receptors for each of the primary neurotransmitters/neuromodulators and their associated effecto systems. Describe how synaptic function changes in response to chronic administration of agonists, antagonists and uptake blockers. Describe the processes of receptor sensitization and desensitization and provide examples of how these processes may be induced. Identify the molecular, cellular, and biochemical sites where drugs can act to affect neuronal function. Define the blood brain barrier and list the considerations that determine whether a drug will gain access to the central nervous system. List areas of the brain that are essentially outside the blood brain barrier and functions of these regions.

4.3 Drugs for the Management of Neurodegenerative Diseases and Treatment of Parkinson Disease		
Recommended Curriculum Equivalent: 1 hr		
4.3.1 Drug Classes and Drugs		
Dopaminergic	Anticholinergic	Other
CARBIDOPA dopamine (not used clinically for PD) ENTACAPONE L-DOPA PRAMIPEXOLE RASAGILINE ROPINIROLE SELEGILINE apomorphine	BENZTROPINE trihexyphenidyl	amantadine
4.3.2 Content Recommendations		
4.3.2.1 Physiology and pathophysiology Describe the major anatomical pathways and neurotransmitter systems involved in control of motor function. Discuss current hypotheses about the etiology and pathophysiology of Parkinson's disease. Describe similarities and differences between idiopathic and iatrogenic Parkinsonism.		
4.3.2.2 Pharmacodynamics Describe the mechanisms of action of the drugs used for Parkinson's disease. Discuss the proposed mechanisms by which monoamine oxidase inhibitors may slow disease progression.		
4.3.2.3 Pharmacokinetics Apply knowledge of the specific pharmacokinetic properties of various dopaminergic drugs as it relates to their therapeutic use and mechanisms of action.		
4.3.2.4 Therapeutic uses Describe the rationale for the use of levodopa in Parkinson's disease and its limitations as the disease progresses. Discuss the justification for the combined use of levodopa with a peripheral L-amino acid decarboxylase inhibitor and how it alters levodopa's therapeutic and adverse effect profiles. Discuss the therapeutic use and rationale for using direct dopamine receptor agonists, anticholinergics, monoamine oxidase inhibitors, and catechol-O-methyltransferase inhibitors.		
4.3.2.5 Adverse effects, drug interactions and contraindications Explain the major adverse effects of the drugs used for the management of Parkinson's disease. Explain how selective monoamine-B inhibitors circumvent causing the hypertensive crisis associated with non-selective monoamine inhibitors.		

4.4 Drugs for the Treatment of Alzheimer Disease

Recommended Curriculum Equivalent: 0.7 hr

4.4.1 Drug Classes and Drugs

Cholinesterase Inhibitors	NMDA receptor antagonist	Amyloid-Beta Monoclonal Antibodies
DONEPEZIL galantamine rivastigmine	MEMANTINE	aducanumab

4.4.2 Content Recommendations

4.4.2.1 Physiology and pathophysiology

Describe the major anatomical pathways and neurotransmitters involved in the pathophysiology of Alzheimer's disease.

4.4.2.2 Pharmacodynamics

Describe the mechanism of action of drugs used for the management of Alzheimer's disease.

4.4.2.3 Pharmacokinetics

Apply knowledge of the specific pharmacokinetic properties of the drugs used for the management of Alzheimer's disease as it relates to their administration and therapeutic use.

4.4.2.4 Therapeutic uses

Discuss the rationale for using cholinesterase inhibitors and NMDA receptor antagonist in the management of Alzheimer's disease and their limitations

Describe the criteria used to classify the stages of Alzheimer's disease and relate this to the initiation of therapy of cholinesterase inhibitors and NMDA receptor antagonist

Relate the effectiveness of cholinesterase inhibitors and NMDA receptor antagonist to their therapeutic use.

Discuss the limited efficacy and controversial approval of aducanumab

4.4.2.5 Adverse effects, drug interactions and contraindications

Compare and contrast the significant adverse effects of cholinesterase inhibitors versus NMDA receptor antagonist for Alzheimer's disease.

4.5 Drugs for the Treatment of Huntington Disease and Amyotrophic Lateral Sclerosis

Recommended Curriculum Equivalent: 0.3 hr

4.5.1 Drug Classes and Drugs

Dopamine-depleting agents	Atypical antipsychotics	Disease-modifying
TETRABENAZINE	risperidone olanzapine aripiprazole	riluzole edaravone

4.5.2 Content Recommendations

4.5.2.1 Physiology and pathophysiology

Describe the major anatomical pathways and neurotransmitters involved in the pathophysiology of Huntington's disease and amyotrophic lateral sclerosis (ALS).

Describe Huntington's Chorea and discuss drugs available for its treatment and their effectiveness.

4.5.2.2 Pharmacodynamics

Describe the mechanism of action of drugs used for the management of Huntington's disease and ALS

4.5.2.3 Therapeutic uses

Discuss the use of antidopaminergic agents in the management of Huntington's disease and the role of atypical antipsychotics in disease management.

Describe the rationale for using disease-modifying agents for the management of ALS and its limitations.

4.5.2.4 Adverse effects, drug interactions and contraindications

Explain the major adverse effects of the drugs used for the management of Huntington's disease and ALS.

Compare and contrast the significant adverse effects of antidopaminergic agents versus the use of atypical antipsychotics for Huntington's disease.

4.6 Drugs for the Treatment of Mental Health Disorders and Psychoses

Recommended Curriculum Equivalent: 1.5 hr

4.6.1 Drugs	
Primary	Secondary
CHLORPROMAZINE ARIPIPRAZOLE CLOZAPINE FLUPHENAZINE HALOPERIDOL OLANZAPINE RISPERIDONE	paliperidone perphenazine quetiapine thiothixene ziprasidone

4.6.2 Content Recommendations

4.6.2.1 Physiology and pathophysiology

Describe schizophrenia and discuss the theories regarding the underlying neurochemical/genetic/developmental basis.
Contrast the actions of phenothiazines and haloperidol with those of 2nd and 3rd generation antipsychotics and the implications for theories of the mechanisms of antipsychotic actions.

4.6.2.2 Pharmacodynamics

Discuss current theories regarding the therapeutic mechanisms of action of antipsychotic drugs, including acute and chronic effects on major dopaminergic and serotonergic systems in the CNS.

4.6.2.3 Therapeutic uses

Compare the effectiveness of classical and atypical antipsychotics in the treatment of both positive and negative symptoms of schizophrenia.
Discuss cognitive impairments and lack of efficacious treatments.
List uses of antipsychotic drugs for indications other than schizophrenia.
Discuss the use of dopamine antagonists in Tourette's syndrome.

4.6.2.4 Adverse effects, drug interactions and contraindications

Differentiate the side effect profiles of low potency vs high potency classical (1st generation) antipsychotics and provide an explanation for these differences.
Discuss the major area in which atypical (2nd and 3rd generation) antipsychotic drug side effect profiles differ from those of classical (1st generation) antipsychotics, the nature of the differences and the mechanistic basis for the differences.
List the major side effects of each of the primary drugs.
Describe the time course, signs and symptoms of antipsychotic drug-induced dyskinesias (dystonia, akathisia, parkinsonism, tardive dyskinesia), and their management and treatment.
Describe neuroleptic malignant syndrome and its management and treatment.

4.7 Drugs for the Treatment of Mood Disorders and Anxiety

Recommended Curriculum Equivalent: 2.5 hr

4.7.1 Drug Classes and Drugs for Depression

Monoamine uptake inhibitors (SSRIs and SNRIs)	Tricyclic antidepressants (TCAs)	Monoamine oxidase inhibitors (MAOIs)	Others NMDA antagonist* GABA-A agonist**
fluoxetine (SSRI) paroxetine (SSRI) sertraline (SSRI) escitalopram (SSRI) vilazodone* venlafaxine (SNRI) duloxetine (SNRI) * Additional actions on receptors	imipramine desipramine amitriptyline nortriptyline protriptyline	phenelzine tranylcypromine	trazodone bupropion nefazadone **brexanolone *esketamine

4.7.2 Drug Classes and Drugs for Bipolar Disorders

Lithium	Anticonvulsants	Antipsychotics
lithium carbonate lithium citrate	carbamazepine lamotrigine valproic acid	aripiprazole olanzapine risperidone

4.7.3 Drug Classes and Drugs for Anxiety Disorders

Antidepressants	Benzodiazepines	Serotonin receptor agents	Others
fluoxetine sertraline	alprazolam diazepam lorazepam	buspirone	doxepin hydroxyzine

4.7.4 Content Recommendations

4.7.4.1 Physiology and pathophysiology

Describe the concept of behavioral affect, the current neurochemical and neurotrophic theories regarding depressive disorders and how they can be altered by drugs.
Define depression and bipolar disorder (1 & 2) and list the symptoms, signs and causes.
Define anxiety and list the types of anxiety disorders.

4.7.4.2 Pharmacodynamics

List the major classes of antidepressant drugs and their primary cellular targets. (TCAs, SSRIs, SNRIs, atypical antidepressants, and MAO inhibitors).
Discuss the mechanisms that could account for the delay in the onset of therapeutic actions of antidepressants.
List the drugs used to treat bipolar disorder and mechanisms of action where known.
List the drugs used to treat anxiety disorders.

4.7.4.3 Pharmacokinetics

Contrast the pharmacokinetics of the different classes of antidepressant drugs.
Discuss the importance of active metabolite formation, and how pharmacokinetics is relevant to switching from one medication to another.
The therapeutic index of lithium is low, and the monitoring of plasma lithium levels is critical to achieve a therapeutic level and avoid toxicity.

4.7.4.4 Therapeutic uses

Discuss the utility of the various classes of antidepressants for other indications: obsessive compulsive disorder, panic disorder, post-traumatic stress disorder (PTSD), neuropathic pain, smoking cessation, enuresis and generalized anxiety disorder.
Discuss the use of anticonvulsants and lithium in bipolar disorder
Discuss the utility of benzodiazepines and antipsychotics in anxiety disorders.
Discuss the use of herbal antidepressants such as St. John’s wort.
Describe factors involved in the selection of appropriate drug(s) for a given patient.

4.7.4.5 Adverse effects, drug interactions and contraindications

Describe and compare the most common adverse effects of the major classes of antidepressants, and where known, explain the mechanism for these effects. Identify significant drug and dietary interactions.
Describe the signs and symptoms of lithium toxicity.

Describe the signs and symptoms of tricyclic antidepressant toxicity and serotonin syndrome and their appropriate treatment.
Discuss possible drug interactions with St. John's wort.

Notes

There should be caution in use of St. John's wort due to induction of CYP3A4 and loss of therapeutic efficacy of drugs metabolized by this pathway that are being administered concurrently. Similarly, there should be caution regarding serotonin syndrome if St. John's wort is used concurrently with prescribed SSRI drugs.
Care should be taken in raising the dose of SSRI abruptly due to increased risk of a rage reaction, especially within the first 2 weeks of dose change and concurrent ingestion of ethanol beverages.
** Esketamine is administered intranasally for treatment-resistant depression.
*Brexanolone has a specific use in treating severe post-partum depression

4.8 Drugs for the Treatment of Sleep Disorders

Recommended Curriculum Equivalent: 1 hr

4.8.1 Drugs

Primary	Secondary
ESZOPICLONE RAMELTEON SUVOREXANT ZALEPLON ZOLPIDEM	estazolam flurazepam lemborexant quazepam tasimelteon temazepam triazolam

4.8.2 Content Recommendations

4.8.2.1 Physiology and pathophysiology

Briefly describe the stages of sleep and the neurotransmitters and pathways mediating sleep including the roles of melatonin and orexin.
Discuss our current understanding of narcolepsy and possible role of immunological mechanisms impairing orexin signaling.

4.8.2.2 Pharmacodynamics

Describe the effects of the GABA-enhancing agents, melatonin receptor agonists and orexin receptor antagonists for the treatment of insomnia.
Discuss the action of stimulants for the treatment of narcolepsy.

4.8.2.3 Pharmacokinetics

Understand differences in the pharmacokinetic profiles and relationships among the benzodiazepines.

4.8.2.4 Therapeutic uses

Discuss our current understanding of insomnia and the hypersomnias and the approaches used to treat these disorders.

4.8.2.5 Adverse effects, drug interactions and contraindications

List the issues detracting from the use of benzodiazepines for insomnia, including REM suppression, daytime hangover and anterograde amnesia.
Understand drug interactions with many of these compounds as a consequence of their metabolism by CYP3A4.

4.9 Drugs for the Treatment of ADHD	
Recommended Curriculum Equivalent: 1 hr	
4.9.1 Drugs	
Primary	Secondary
AMPHETAMINE DEXTROAMPHETAMINE LISDEXAMFETAMINE METHYLPHENIDATE	atomoxetine guanfacine viloxazine
4.9.2 Content Recommendations	
4.9.2.1 Physiology and pathophysiology Discuss the presumed physiological basis for the use of stimulants and nonstimulants for attention deficit hyperactivity disorder.	
4.9.2.2 Pharmacodynamics Describe the cellular mechanisms of action of the stimulant and nonstimulant drugs.	
4.9.2.3 Pharmacokinetics Discuss the role of pharmacokinetics in determining the dosing regimen for the different methylphenidate preparations. Define a prodrug and understand possible advantages of lisdexamfetamine as a prodrug.	
4.9.2.4 Therapeutic uses List the criteria for the diagnosis of ADHD.	
4.9.2.5 Adverse effects, drug interactions and contraindications Discuss the adverse and toxic effects of stimulants with particular attention to cardiovascular problems, drug dependence and substance abuse. Discuss the adverse effects of the nonstimulants with attention to the induction of somnolence.	

4.10 Drugs Used for Seizures			
Recommended Curriculum Equivalent: 1.5 hr			
4.10.1 Drug Classes and Drugs			
Drugs Enhancing GABA	Drugs Blocking Na^+ Channels	Drugs Blocking Ca^{2+} channels	Others (SV_{2a} ,K^+, & glutamate)
diazepam (PAM) clonazepam (PAM) lorazepam (PAM) valproic acid tiagabine (uptake) vigabatrin (GABA-T) phenobarbital (PAM+)	phenytoin carbamazepine lamotrigine lacosamide (slow)	ethosuximide (t-type) gabapentin (n-type) pregabalin (n-type)	levetiracetam (sv2a) perampanel (glut) ezogabine (k+) acetazolamide cannabidiol fenfluramine (5-HT)
4.10.2 Content Recommendations			
4.10.2.1 Physiology and pathophysiology Describe the pathophysiology of seizures, and the types of the most common seizure forms (to include generalized tonic clonic, absence, and status epilepticus) Discuss briefly each of the following with respect to their possible relevance to the initiation and spread of seizure activity: mirror foci, kindling, post-tetanic potentiation, long-term potentiation, paroxysmal depolarizing shift, and channelopathies.			
4.10.2.2 Pharmacodynamics List the major classes of antiseizure drugs, the seizure types against which they are effective, their cellular mechanisms of action, and how these actions might be relevant to their roles as antiseizure agents. Discuss the role of the different GABA receptor neurotransmitter mechanisms in the action of gabaergic anti-seizure agents. Differentiate between anticonvulsant and antiepileptic actions on the basis of prophylaxis and acute therapy and differentiate seizures from epilepsy. Describe the principles of antiepileptic therapy to include monotherapy vs. poly drug therapy, withdrawal of drug therapy and the factors involved in epilepsy treatment failures.			
4.10.2.3 Pharmacokinetics Explain why the clearance of phenytoin changes with dose. Discuss the rationale for the common practice of monitoring plasma concentrations of many antiepileptic drugs.			
4.10.2.4 Therapeutic uses Describe the type of seizure use for each antiseizure medications. Define status epilepticus and explain how it is managed pharmacologically. Discuss the therapeutic use of antiseizure drugs for conditions other than epilepsy, including their use as analgesics and as mood stabilizers.			
4.10.2.5 Adverse effects, drug interactions and contraindications List and describe the adverse and teratogenic effects of the major antiseizure drugs (especially valproic acid). List the antiseizure medications that induce hepatic enzymes and describe the consequences for treatment of epilepsy and for interactions with drugs used for other conditions.			
Notes Several antiseizure drugs have more than one mechanism of action (e.g., valproic acid) but are listed by their major action. Most antiseizure drugs that act on Na+ channels enhance the fast inactivated state except lacosamide. Treatment with anticonvulsant drugs is most often long-term leading to adverse effects and can result in lack of patient adherence. Sudden unexpected death in epilepsy (SUDEP) is a major cause of long-term mortality but effective drugs have not yet been validated. Effective therapy for epilepsy is not achieved in 30% of patients, which leads to the search for and approval of new drugs (e.g., cenobamate) as well as neurosurgery.			

4.11 Drugs for the Treatment of Spasticity Disorders	
Recommended Curriculum Equivalent: 1 hr	
4.11.1 Drugs	
Primary	Secondary
BACLOFEN DANTROLENE DIAZEPAM	botulinum toxin clonidine clonazepam

METAXALONE METHOCARBAMOL TIZANIDINE	cyclobenzaprine

4.11.2 Content Recommendations

4.11.2.1 Physiology and pathophysiology

Discuss the pathophysiological basis of rigidity, spasticity, muscle spasm and the classes of agents used to promote skeletal muscle relaxation.

4.11.2.2 Pharmacodynamics

Understand the role of spinal GABA and α_2 receptors in mediating skeletal muscle contraction and drug actions. Describe the biochemical processes involved in skeletal neuromuscular transmission and understand how drugs interfere with these processes.

4.11.2.3 Pharmacokinetics

Understand why some of these agents can be administered orally while others must be injected either intravenously or directly into muscle.

4.11.2.4 Therapeutic uses

Discuss the use of these agents for rigidity, spasticity, and muscle spasms.

4.11.2.5 Adverse effects, drug interactions and contraindications

Discuss limitations to the use of the oral medications including the development of tolerance and sedation.

4.12 Drugs Used for Pain Management and General Anesthetics

Recommended Curriculum Equivalent: 1.5 hr

4.12.1 Drug Classes and Drugs

Inhaled gases	Intravenous agents	Adjuncts
DESFLURANE NITROUS OXIDE (N_2O) SEVOFLURANE halothane (historic)	dexmedetomidine ETOMIDATE KETAMINE PROPOFOL thiopental (historic)	fentanyl midazolam morphine REMIFENTANIL sufentanil

4.12.2 Content Recommendations

4.12.2.1 Physiology and pathophysiology

Relate Fick's law of diffusion to the use of inhaled anesthetics.

4.12.2.2 Pharmacodynamics

Identify the receptor targets as it relates to the mechanisms of action of inhalation anesthetics and of intravenous anesthetics.
Apply the Meyer-Overton rule to the potency of inhaled anesthetics.
Define minimum alveolar concentration (MAC) and explain how it is used in anesthesiology.
Compare and contrast the potencies of inhaled anesthetics.

4.12.2.3 Pharmacokinetics

Explain the role of alveolar pressure on the absorption of inhaled anesthetics
Define the terms alveolar fractional concentration and inspired concentration an relate the ratio to onset for inhaled anesthetics.
Define oil/gas partition coefficient and blood/gas partition coefficient and relate these concepts to onset of action and rate of recovery for inhaled anesthetics.
Compare and contrast speed of onset and duration of action for the different types of general anesthetics.
Describe the relative roles of distribution and metabolism in determining speed of onset and duration of action of intravenous anesthetics.
Define context-sensitive half-time and relate it to the use of intravenous anesthetics.

4.12.2.4 Therapeutic uses

Define the terms general anesthesia and balanced anesthesia.
State the objectives of general anesthesia, characteristics of an ideal anesthetic, and the stages of general anesthesia.
Discuss relative advantages and disadvantages of using intravenous versus inhaled anesthetics.
Relate the unique pharmacological profile of the various inhaled and intravenous anesthetics to their clinical application.
Apply knowledge of adjunct agents to their role in general anesthesia.

4.12.2.5 Adverse effects, drug interactions and contraindications

Explain the major adverse effects of the inhaled and intravenous anesthetics.
Explain the major adverse effects of drugs commonly used as adjuncts to anesthesia.
Indicate how the concomitant use of adjunct agents may affect the concentrations of inhaled anesthetics used to maintain the anesthesia.
Describe the effects of inhaled anesthetics on cardiovascular, respiratory, and skeletal muscle function.
Discuss the adverse effects of intravenous anesthetics that may limit their therapeutic use.

Notes: Halothane is still widely used in the developing world. It is a core medicine in the World Health Organization's "Essential Drugs List."

4.13 Local Anesthetics

Recommended Curriculum Equivalent: 1 hr

4.13.1 Drugs

Primary	Secondary
BENZOCAINE BUPIVACAINE LIDOCAINE PROCAINE ROPIVACAINE	articaine cocaine prilocaine tetracaine

4.13.2 Content Recommendations

4.13.2.1 Physiology and pathophysiology

Review the concept of weak bases, the Henderson-Hasselbalch equation, and drug transport across membranes.
Discuss the relevance of isoforms of the voltage-gated sodium channel to the development of new local anesthetics.
Describe the ionic basis of the action potential.

4.13.2.2 Pharmacodynamics

Discuss the mechanism of action of local anesthetics, including a description of how the action of benzocaine differs from that of other primary agents.

4.13.2.3 Pharmacokinetics

Explain how the actions of clinically used anesthetics might be influenced by the frequency of impulse transmission in peripheral nerves, size and class of the peripheral axons, pH, and by the vascularity of the injected area.

4.13.2.4 Therapeutic uses

Describe the common routes of administration of local anesthetics. List anesthetics that cannot be used topically, that cannot be used for infiltration. Explain why these routes are not effective.
Describe methods used to restrict local anesthetics to a desired site of action and indicate how these methods reduce adverse effects.
Compare and contrast the advantages and potential adverse effects of epidural and intrathecal use of local anesthetics with similar use of opioids (see “opioid analgesics, agonist-antagonists, and antitussives).

4.13.2.5 Adverse effects, drug interactions and contraindications

List the common adverse effects of local anesthetics and indicate appropriate treatments should they occur.
List the significant differences between amide and ester-type local anesthetics.

4.14 Opioid Analgesics

Recommended Curriculum Equivalent: 1.5 hr

4.14.1 Drug Classes and Drugs

Agonists	Partial Agonist/Antagonist	Antagonists
CODEINE FENTANYL HYDROCODONE HYDROMORPHONE METHADONE MORPHINE OXYCODONE OXYMORPHONE TRAMADOL meperidine (historic)	BUPRENORPHINE	NALOXONE NALTREXONE

4.14.2 Content Recommendations

4.14.2.1 Physiology and pathophysiology

Describe the major anatomical pathways, mechanisms, and neurotransmitter systems involved in nociceptive transmission including peripheral and central sensitization.
Explain descending inhibitory regulation of nociceptive transmission.
Identify the peripheral and central portions of the nociceptive pathway that can be modified by opioid receptor activation.
Explain the difference between nociception and pain.
Describe the different aspects of pain including sensory, emotional, and cognitive components and the consequences of inadequately managed pain.
Describe the differences between acute, chronic inflammatory (nociceptive), and chronic neuropathic pain.
Describe the influence of opioid receptors on the pupillary light reflex as well as the GI, genitourinary, and respiratory systems.
Identify the endogenous opioid peptides and opioid receptor subtypes along with their signal transduction mechanism.

4.14.2.2 Pharmacodynamics

Explain the molecular mechanism by which opioid receptor activation modulates nociceptive transmission.
Identify the influence of opioid receptor subtype activation on peripheral, spinal, and supraspinal analgesia.
Identify opioid agonists associated with histamine release and explain the impact on adverse effects.
Compare the receptor effects of a full and partial agonist.
Explain the impact of buprenorphine's slow dissociation from the receptor on the ability of naloxone to reverse its effects.
Explain the difference between tramadol and other opioid receptor agonists in terms of their mechanisms of action.

4.14.2.3 Pharmacokinetics

Describe the impact of the first-pass effect on morphine's absorption and morphine's influence on absorption of other drugs.
Explain the impact of lipophilicity on different opioid agonist onset, duration of action, addictive potential, and administration.
Describe the distribution of opioids in the body, including their ability to cross the blood-brain barrier and the placenta.
Identify the primary metabolites of morphine and the impact of renal insufficiency.
List opioid agonists that are metabolized to morphine and indicate the salient differences in their pharmacology from that of morphine.
Describe the impact of CYP2D6 isoforms on codeine's therapeutic use and adverse effects.
Explain how the half-life of methadone impacts its therapeutic use.

4.14.2.4 Therapeutic uses

Present the clinical indications for the opioids and opioid antagonists and explain the basis for their use.
Discuss selection of appropriate therapeutic agents based on severity and type of pain; consider misuse potential versus therapeutic benefits of various opioids; and demonstrate awareness of legal and ethical issues in prescribing of opioids.
Discuss the rationale for using combinations of opioid analgesics and NSAIDS, aspirin, or acetaminophen along with special concerns of combination formulation with acetaminophen.
Discuss the salient differences between naloxone and naltrexone and how these are reflected in clinical use of these drugs.
Discuss how the combination of naloxone with opioid analgesics in oral and sublingual preparations permits opioid action yet decreases misuse liability.
Discuss diversion and misuse of prescription opioids and approaches to minimize these occurrences.

4.14.2.5 Adverse effects, drug interactions and contraindications

List adverse effects of morphine on CNS, GI-biliary, respiratory, genitourinary, and cardiovascular systems.
Explain the differences in adverse effects of methadone and buprenorphine.

Identify and explain signs of opioid toxicity and discuss its management.
List and explain drug class interactions with morphine and buprenorphine particularly those affecting respiratory depression.
Describe the characteristics of opioid tolerance including the actions of morphine that do and do not show significant tolerance.
Describe opioid withdrawal syndrome and how it differs from that for sedative-hypnotics.
Explain precipitated withdrawal and indicate under what circumstances it might occur following the clinical use of opioid analgesics or antagonists.
Discuss misuse liability for opioids and how it differs among the various drugs.

4.15 Treatments for Neuropathic Pain			
Recommended Curriculum Equivalent: 0.5 hr			
4.15.1 Drug Classes and Drugs			
Gabapentanoids	Other Antiepileptic	SNRI	TCA
GABAPENTIN PREGABALIN	CARBAMAZEPINE	DULOXETINE VENLAFAXINE	AMITRIPTYLINE
4.15.2 Content Recommendations			
4.15.2.1 Physiology and pathophysiology Describe descending pain modulation. Explain the role of norepinephrine and serotonin in nociceptive transmission. Describe neuropathic pain in terms of its etiology, including the role of Aβ fibers, and presentation and contrast that with inflammatory (nociceptive) pain.			
4.15.2.2 Pharmacodynamics Describe the mechanism of action of the different drugs/drug classes in treating neuropathic pain.			
4.15.2.3 Therapeutic uses Contrast the use of these drug classes with opioids for the treatment of neuropathic pain. List other therapeutic uses for each of the drug classes.			
4.15.2.4 Adverse effects, drug interactions and contraindications Describe the primary adverse effects associated with each drug. Explain concerns of combining gabapentanoids with opioids and benzodiazepines. Discuss diversion and misuse of gabapentin.			

4.16 Treatments for Primary Headache Disorders			
Recommended Curriculum Equivalent: 1 hr			
4.16.1 Drug Classes and Drugs for Migraine			
NSAIDS	Acetaminophen	Triptan	CGRP Antagonist
IBUPROFEN KETOROLAC	ACETAMINOPHEN	SUMATRIPTAN dihydroergotamine (historical)	RIMEGEPANT ERENUMAB
Beta Blocker	TCA	Antiepileptic	
PROPRANOLOL	AMITRIPTYLINE	TOPIRAMATE	
4.16.2 Drug Classes and Drugs for Tension			
NSAIDS	Acetaminophen	TCA	Antiepileptic
IBUPROFEN	ACETAMINOPHEN	AMITRIPTYLINE	GABAPENTIN
4.16.3 Drug Classes and Drugs for Cluster			
Triptan	Calcium Channel Blocker	Other	
SUMATRIPTAN	VERAPAMIL	OXYGEN	
4.16.4 Drug Classes and Drugs for Trigeminal Neuralgia			
Antiepileptic			
GABAPENTIN CARBAMAZEPINE			
4.16.5 Content Recommendations			
4.16.5.1 Physiology and pathophysiology Differentiate primary headache disorders (migraine, tension, cluster, and trigeminal neuralgia) in terms of presentation and diagnostic criteria. Explain the role of neurogenic inflammation, CGRP, and vasodilation in migraines. Explain the modulatory role of the 5-HT1B/1D receptor on CGRP release.			
4.16.5.2 Pharmacodynamics Explain the mechanism of action of each of the drug/drug classes.			
4.16.5.3 Pharmacokinetics Compare the administration of small molecule CGRP antagonists with CGRP receptor blocking antibodies.			
4.16.5.4 Therapeutic uses Differentiate the acute vs preventative treatments for migraine, tension, and cluster headaches. Compare the appropriate use of ibuprofen with ketorolac. Describe the treatment of trigeminal neuralgia. List other therapeutic uses for each of the drug classes.			
4.16.5.5 Adverse effects, drug interactions and contraindications Describe the primary adverse effects associated with each drug.			

4.17 Ethanol, other alcohols, and Drugs for Alcohol Use Disorder

Recommended Curriculum Equivalent: 0.3 hr

4.17.1 Drugs

Primary	Secondary
ACAMPROSATE ETHANOL FOMEPIZOLE METHANOL NALTREXONE	disulfiram ethylene glycol gabapentin topiramate

4.17.2 Content Recommendations

4.17.2.1 Physiology and pathophysiology

Describe the acute CNS actions of ethanol and discuss their relationship to blood alcohol levels.
Describe the effects of chronic alcohol on sleep.
Describe the fetal alcohol syndrome and approaches to prevention.

4.17.2.2 Pharmacodynamics

Discuss current theories about the mechanism of action of alcohol in the CNS including actions on $GABA_A$ and N-methyl-D-aspartate (NMDA) receptors.

4.17.2.3 Pharmacokinetics

Describe the pharmacokinetics of ethanol, its absorption, distribution, metabolism and excretion.
List the effects of chronic (moderate or high) alcohol use on alcohol metabolism and organ function.

4.17.2.4 Therapeutic uses

Summarize the therapeutic applications of ethanol.
Discuss the treatment options for acute intoxication by ethanol or other alcohols, and for the ethanol abstinence syndrome.
Discuss the use of disulfiram, naltrexone and acamprosate in the treatment of chronic alcoholics. Describe their effects and the mechanistic rationale for their use.

4.17.2.5 Adverse effects, drug interactions and contraindications

Describe the acute and chronic organ toxicities of ethanol, methanol, and higher alcohols (e.g. ethylene glycol).
List drugs with which ethanol shows cross-tolerance and cross-dependence.
List drugs, both prescription and over the counter, that would entail a patient refraining from the use of alcoholic beverages. Explain the nature of the potential interactions.
List the signs and symptoms of chronic alcoholism and the ethanol abstinence syndrome and compare and contrast the latter with abstinence syndromes following chronic use of barbiturates, benzodiazepines, or opioids.
Compare and contrast morbidity and mortality of ethanol use with that for other drugs of abuse.

Notes

For the most part, there is no longer an acceptable therapeutic use of ethanol. It was sometimes used in older patients to stimulate gastric acid production prior to a meal. Acutely, it can be used as a second line treatment by injection for trigeminal neuralgia.
Fomepizole has evolved into the treatment of choice for overdose with methanol or ethylene glycol. In the absence of fomepizole, ethanol may be a reasonable treatment for methanol or ethylene glycol overdose, but control of concentration after ingestion is problematic, and exacerbation of CNS depression is a major concern.
Disulfiram was widely used to treat alcoholism but its use is potentially problematic because its mechanism involving interacting with ethanol to produce an unpleasant and potentially toxic syndrome.

4.18 Psychoactive Compounds and Drugs for Substance Use Disorders

4.18.1 General Principles

Recommended Curriculum Equivalent: 0.2 hr

4.18.2 Content Recommendations

4.18.2.1 Physiology and pathophysiology

Define and differentiate tolerance, physical dependence and substance use disorders based on DSM-V criteria.
Discuss the roles of drug craving and reward vs. avoidance of withdrawal in initiation and maintenance of substance abuse and dependence.
Define conditioned withdrawal and precipitated withdrawal and indicate their relevance to substance dependence and its treatment.
Discuss how pharmacokinetics influences abuse liability and withdrawal syndromes. Compare patterns and effects of substance abuse for stimulants, opioids, sedative-hypnotics, anxiolytics cannabinoids and hallucinogens.

4.18.3 Psychostimulants

Recommended Curriculum Equivalent: 0.5 hr

4.18.3.1 Drugs

Primary	Secondary
AMPHETAMINES BUPROPION CAFFEINE COCAINE METHAMPHETAMINE METHYLPHENIDATE NICOTINE VARENICLINE	cathinone and analogs ephedrine phentermine

4.18.3.2 Content Recommendations

4.18.3.2.1 Pharmacodynamics

Discuss current theories of the mechanisms of action of the stimulant drugs listed above.

4.18.3.2.2 Therapeutic uses

Discuss the use of varenicline, bupropion, and various formulations of nicotine to treat nicotine dependence.
Describe the treatment for overdose on stimulant drugs along with the major clinical indications of overdoses.
Discuss current thoughts on potential treatments for stimulant drug dependence.

4.18.3.2.3 Adverse effects, drug interactions and contraindications

Compare abuse liability among the various listed stimulants and among available preparations of each drug.
Discuss adverse effects of misused and abused stimulants. Compare the behavioral differences in the repeated use of cocaine and amphetamine
Discuss how the pharmacokinetics of cocaine and amphetamine contribute to frequent dosing.
Discuss the addictive properties of nicotine, and the adverse effects of nicotine and other constituents of tobacco.
Compare and contrast patterns of substance misuse and abuse of stimulants with those of other drugs of abuse.
Compare and contrast differences between cocaine and amphetamine in their pharmacological mechanisms of action
Compare and contrast morbidity and mortality of misuse and abuse of stimulants with those of other drugs of abuse.
Compare and contrast patterns of tolerance and dependence, and the withdrawal syndromes for stimulants with those of other drugs of abuse.
Discuss side effects of varenicline and contraindications of bupropion.

4.18.4 Hallucinogens and Psychedelics	
Recommended Curriculum Equivalent: 0.5 hr	
4.18.4.1Drugs	
Primary	Secondary
LYSERGIC ACID DIETHYLAMIDE (LSD) MDMA (methylene dioxymethamphetamine) – "Ecstasy/Molly" MESCALINE PSILOCYBIN PHENCYCLIDINE (PCP) KETAMINE "Special K"	atropine bath salts (methylenedioxypyrovalerone) bufotenine (dimethyltryptamine (ibogaine) salvia scopolamine
4.18.4.2 Content Recommendations	
4.18.4.2.1 Physiology and pathophysiology Describe salient differences among the behavioral and hallucinogenic effects of the various drugs and compare and contrast the drug-induced states with endogenous psychoses and with amphetamine-induced psychosis. Discuss the variability in inter-individual responses to hallucinogens and the interaction between the social setting in which hallucinogens are taken and their behavioral effects. Describe how these drugs differ from drugs of abuse in terms of dependence, addiction, tolerance and reward mechanisms as well as withdrawal. Discuss potential medical uses of hallucinogens and psychedelics.	
4.18.4.2.2 Pharmacodynamics List the hallucinogens with primary actions on 5-HT2A receptors, those that are NMDA receptor antagonists, and muscarinic receptor antagonists, and describe their mechanisms of action.	
4.18.4.2.3 Pharmacokinetics Describe how the pharmacokinetics of different drugs may influence their duration of action and their detection by screening tests for illicit drug use.	
4.18.4.2.4 Adverse effects, drug interactions and contraindications Discuss tolerance to and cross-tolerance among the various hallucinogens. Describe the toxidromes expected for LSD, MDMA, PCP, and belladonna alkaloids. Discuss general principles of treatment for patients with known ingestion of hallucinogens.	
Notes For the most part, treatment of consequences relating to acute ingestion of these drugs defaults to supportive care and patient placement in a quiet, nonthreatening environment.	

4.18.5 Marijuana and Cannabinoids	
Recommended Curriculum Equivalent: 0.5 hr	
4.18.5.1 Drugs	
Primary	Secondary
CANNABIDIOL (CBD) DELTA-9-TETRAHYDROCANNABINOL (THC) DRONABINOL MARIJUANA	designer cannabinoids (delta-8-THC, THC-O) hashish K-2 nabilone spice
4.18.5.2 Content Recommendations	
4.18.5.2.1 Physiology and pathophysiology Discuss the endogenous cannabinoids, how they differ from classical neurotransmitters/neuromodulators, their receptors, and the current hypotheses about their functional roles.	
4.18.5.2.2 Pharmacodynamics List the psychological, physiological and pharmacologic effects of smoking marijuana; or ingesting cannabinoids. Compare and contrast patterns of marijuana use with that of other drugs of abuse.	
4.18.5.2.3 Pharmacokinetics Compare and contrast pharmacokinetics and effects of inhaled cannabinoids with those of ingested cannabinoids.	
4.18.5.2.4 Therapeutic uses List the approved therapeutic indications for dronabinol. Discuss the current controversy over the use of medical marijuana vs. the use of dronabinol or nabilone, and proposed therapeutic actions aside from those currently approved for dronabinol. Describe the effects of cannabinoid receptor antagonists and their potential uses.	
4.18.5.2.5 Adverse effects, drug interactions and contraindications Describe symptoms of cannabis use disorder. Discuss signs, symptoms and treatment of acute marijuana/cannabinoid overdose. List potential chronic health effects of heavy marijuana/cannabinoid use. Understand current legal issues related to medical and recreational use of marijuana, especially with respect to federal, state and local laws. Compare and contrast morbidity of marijuana use with that of other drugs of abuse. Compare and contrast tolerance and dependence on marijuana with that for other drugs of abuse.	
Notes With currently available clinical trial evidence, cannabinoids are probably indicated only as second-line treatment for nausea and vomiting associated with cancer chemotherapy that is unresponsive to other more conventional antiemetics. There is suggestive evidence for its efficacy as a co-analgesic to manage terminal pain in a palliative care setting. Clinical trials to assess efficacy and toxicity in patients with severe pain are currently ongoing. Robust clinical trial data to support other claimed human therapeutic indications are currently lacking. Currently, there are major differences in federal and state laws regarding use of medical and recreational marijuana.	

4.19 General Depressants (Sedative/Hypnotics)	
Recommended Curriculum Equivalent: 0.5 hr	
4.19.1 Drugs	
Primary	Secondary
ALPRAZOLAM BUTALBITAL DIAZEPAM FLUNITRAZEPAM CHLORDIAZEPOXIDE GAMMAHYDROXYBUTYRATE (GHB)	secobarbital zolpidem
4.19.2 Content Recommendations	
4.19.2.1 Pharmacodynamics Describe the suggested mechanisms of action of these drugs.	
4.19.2.2 Therapeutic uses Discuss the therapeutic use(s) of the benzodiazepines	

Describe the differences in the therapeutic use of GHB and benzodiazepines.

4.19.2.3 Adverse effects, drug interactions and contraindications

Discuss symptoms and treatment of barbiturate, benzodiazepine and GHB overdose.
Discuss the relative abuse potential of drugs within this class.
Compare and contrast patterns of barbiturate and benzodiazepine abuse with that of other drugs of abuse.
Compare and contrast morbidity and mortality of barbiturate abuse, benzodiazepine abuse, and abuse of other classes of drugs.
Compare and contrast tolerance and dependence, and the nature of the withdrawal syndrome for barbiturates, benzodiazepines, and that for other drugs of abuse.
Describe benzodiazepine dependence and withdrawal

Notes

Benzodiazepine abuse represents one of the largest problems in clinical pharmacology. There is substantial diversion for recreational use, especially in combination with alcohol. Diazepam by mouth is a reasonable therapy for management of the alcohol withdrawal syndrome. Its long half-life serves to reduce the severity of the withdrawal reaction and serves as a self-tapering mechanism when drug doses are stopped.

4.20 Opioids

Recommended Curriculum Equivalent: 0.7 hr

4.20.1 Drug Classes and Drugs

Agonist	Antagonists
BUPRENORPHINE BUPRENORPHINE/NALOXONE FENTANYL HEROIN METHADONE morphine oxycodone	NALOXONE NALTREXONE

4.20.2 Content Recommendations

4.20.2.1 Pharmacodynamics

Describe the pharmacological differences between buprenorphine and the two opioid receptor antagonists

4.20.2.2 Therapeutic uses

Describe dependence, tolerance and withdrawal from opioids
Discuss treatment of opioid overdose in a chronic user of these drugs.
Explain why agonists, partial agonists, and antagonists are used differently in treating opioid use disorder and opioid overdose.
Explain the rationale for using methadone to treat opioid use disorder. List the aspects of methadone's pharmacokinetics and pharmacodynamics that make it useful for this purpose.
Discuss the salient differences between maintenance therapy with methadone and buprenorphine.
Explain why after initiating buprenorphine therapy, maintenance is commonly affected using a combination of buprenorphine and naloxone.
Discuss the rationale and limitations of the use of naltrexone for treating patients with opioid substance dependence.

4.20.2.3 Adverse effects, drug interactions and contraindications

Discuss the development of substance dependence (addiction) on opioids during their use for treatment of pain, differentiating physical dependence from addiction.
Describe patterns of opioid abuse, compare and contrast them with those of other classes of abused drugs.
Discuss the opioid abstinence syndrome, list the signs and symptoms and compare and contrast these with withdrawal from CNS depressants including ethanol and benzodiazepines.

Notes

Use of methadone is particularly problematic in that it prolongs the QTc interval and is dangerous in the patient with underlying cardiac disease and/or receiving therapy with other drugs concurrently that also prolong the QTc interval. Since buprenorphine is a partial agonist, it should not be used concurrently for chronic pain management with a full opioid

agonist due to the increased risk of precipitating an acute opioid withdrawal reaction. Buprenorphine also prolongs the QTc interval.

4.21 Inhalants/Organic Solvents and Gases	
Recommended Curriculum Equivalent: 0.3 hr	
4.21.1 Drugs	
Primary	Secondary
TOLUENE GLUE NITROUS OXIDE	amylnitrite butane carbon tetrachloride fire extinguisher accelerants fluorocarbons gasoline
4.21.2 Content Recommendations	
4.21.2.1 Adverse effects, drug interactions and contraindications Discuss the epidemiology of abuse of inhalants. Describe, in general terms, the effects of organic inhalants and nitric oxide generators and their toxicities.	

5. PULMONARY PHARMACOLOGY
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5. Drugs for the Management of Respiratory Disorders

Recommended Curriculum Equivalent: 1 hr

5.1 Drug Classes and Drugs

5.1.1 Anti-inflammatory Drugs

Glucocorticoids	Immunomodulators		Leukotriene Receptor Antagonists	5-LO Inhibitor
	IL ANTAGONISTS	Anti-IgE		
Inhaled agents: BUDESONIDE BECLOMETHASONE FLUTICASONE MOMETASONE **Systemic agents:** DEXAMETHASONE PREDNISONE	DUPILUMAB RESLIZUMAB	OMALIZUMAB	MONTELUKAST	ZILEUTON

5.1.2 Bronchodilators

β_2 Agonists		Muscarinic Receptor Antagonists		Phosphodiesterase 4 Inhibitors
Short-Acting beta 2 agonists (SABA)	**Long-Acting beta 2 agonists (LABA)**	**Short-acting antimuscarinic agents (SAMA)**	**Long-acting antimuscarinic agents (LAMA)**	Roflumilast
		IPRATROPIUM	TIOTROPIUM	
ALBUTEROL	FORMOTEROL SALMETEROL			

5.2 Content Recommendations

5.2.1 Physiology and Pathophysiology

Describe the role of cyclic AMP, cyclic GMP, leukotrienes, and nitric oxide in regulation of bronchiolar smooth muscle tone and pulmonary vasculature.

Describe the role of phosphodiesterases (PDEs) and their isoenzymes (i.e., PDE4) in the function of bronchiolar smooth muscle and in the inflammatory process.

Characterize the role of inflammation in the pathogenesis of asthma and chronic obstructive pulmonary disease (COPD).

Identify the relationship of bronchial smooth muscle reactivity with the pathogenesis of asthma.

Describe the similarities and differences between asthma and chronic obstructive pulmonary disease.

5.2.2 Mechanisms of action

Describe the molecular mechanism of action of each of the above listed drug classes within the framework of pathogenesis of asthma and COPD.

Based on molecular mechanism of action, distinguish between agents that modify the disease process versus those that relieve symptoms of asthma and COPD.

5.2.3 Actions on organ systems

Distinguish the actions of the above listed agents on bronchial smooth muscle tone and inflammatory processes.

Describe the relevant actions of these drugs on other physiological systems.

5.2.4 Pharmacokinetics

Compare the onset and duration of action of inhaled beta 2 agonists and antimuscarinic agents.

Discuss the relative merits of inhaled versus systemic (oral or intravenous) administration of drugs for the management of both episodic and chronic asthma, as well as COPD.

5.2.5 Adverse effects, drug interactions and contraindications

Discuss the adverse effects and potential contraindications for each class of agents.

Describe why non-steroidal anti-inflammatory drugs (aspirin) can trigger bronchoconstriction when administered to a patient with asthma.

5.2.6 Therapeutic uses

Compare and contrast the role of beta 2 agonists, antimuscarinic agents, systemic and inhaled glucocorticoids, leukotriene inhibitors, and emerging therapies in the management of acute and chronic asthma, as per the latest guidelines.

Describe the management of asthma in special patient populations (e.g., pediatric and pregnant and/or lactating females).

Describe the therapies for preventing and treating exercise-induced asthma.

Describe the role of emerging therapies in the management of asthma and chronic obstructive pulmonary disease.

Describe the complementary therapeutic role of non-pharmacologic approaches in the management of asthma and COPD (e.g., smoking cessation and oxygen).

Notes

Information on many of the drugs in this section may also be found in the Autonomics Section (3).

Information on asthma and COPD is also found in Section 9.7 in the Autacoid Section (9).

Theophylline (a methylxanthine) and cromolyn (a mast cell stabilizer) are mentioned here because of their historical perspective, and frequent appearance on board exams. Both drugs are no longer included on the WHO List of Essential Medications and are considered as last line drugs for the treatment of asthma. According to the GINA (Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention, 2021; available from: www.ginasthma.org. Accessed 10 April 2022), theophylline is not recommended because of low efficacy, high risk of severe side effects and possible drug-drug interactions. Cromolyn is not even mentioned on the GINA guidelines.

It is noteworthy that the clinical guidelines for the treatment of asthma and COPD continuously evolve and are updated yearly. To that end, instructors are urged to consult online sources such as:

- Global Initiative for Asthma. www.ginasthma.org (look for the current treatment report)
- National Asthma Education and Prevention Program. 2020. https://www.nhlbi.nih.gov/health-topics/asthma-management-guidelines-2020-updates

Note also that in addition to asthma and COPD, other diseases affecting respiration may employ these agents (e.g., see relevant sections on antimicrobials and/or neoplasias).

6. CARDIOVASCULAR PHARMACOLOGY
Subcommittee:

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6. CARDIOVASCULAR
Recommended Total Curriculum Equivalent: 15 hrs.
6.1. Content Recommendations for Introduction to Cardiovascular Drugs
6.1.1. Physiology and Pathophysiology: Review of Cardiovascular Physiology (2 hrs equivalent)
1. Review the properties of the heart including contractility (e.g., excitation-contraction coupling) and electrical activity (e.g. the action potential, automaticity, excitability, refractory period, conduction and the relationship to the electrocardiogram). Review the concepts of inotropism, chronotropism, dromotropism as they pertain to mechanisms of action of commonly used drugs. Discuss the mechanisms by which the autonomic nervous system regulates heart rate and contractility. 2. Review the neuroendocrine properties of the heart (both response and output). 3. Discuss mechanisms of myocardial growth, hypertrophy and signal transduction. 4. Review the intrinsic and extrinsic regulation of the cardiovascular system. 5. Describe cardiac and vascular smooth muscle cellular pathobiology including mechanisms of apoptosis and responses to hypoxia, reperfusion, ischemia and mechanical and oxidative stress.

6.2. Drugs Used for the Management of Arrhythmia

Recommended Curriculum Equivalent: 3.0 hrs.

6.2.1. Drug Classes and Drugs

CLASS I
Voltage-gated Na+ channel blockers

Class IA	Class IB	Class IC
PROCAINAMIDE Quinidine Disopyramide	LIDOCAINE Mexiletine	Propafenone Flecainide
CLASS II *Beta antagonists*	**CLASS III** *Voltage dependent K+ channel blockers*	**CLASS IV** *Calcium channel blockers*
ESMOLOL PROPRANOLOL	AMIODARONE Sotalol Ibutilide	DILTIAZEM VERAPAMIL

Other Drugs Used

Management of tachyarrhythmias			***Management of bradyarrhythmias***	
Other specific	***M2 receptor activators***	***Adenosine A1 receptor activators***	***Beta receptor agonists***	***M2 receptor antagonists***
Magnesium	Digoxin	Adenosine	Isoproterenol	Atropine

6.2.2. Content Recommendations for Management of Arrhythmias

6.2.2.1. Physiology and pathophysiology: Introduction to Cardiac Electrophysiology and Pathophysiology

1. Relate the concepts of the ionic basis of the cardiac action potential to the pathophysiology of arrhythmias.
2. Summarize the role of specific ions and ionic conductances in the production and propagation of the cardiac action potential with emphasis on fast (sodium dependent) and slow (calcium dependent) responses and their relevance to specific cardiac tissue types.
3. Differentiate the electrophysiological differences between normal atrial and ventricular cardiac muscle cells and between pacemaker and non-pacemaker cardiac cells.
4. Discuss the temporal relationship between cellular cardiac electrical activity and the electrocardiogram.
5. Specify the pathophysiologic mechanisms of cardiac arrhythmias (abnormal automaticity, triggered rhythms, reentrant rhythms and abnormal impulse conduction).
6. Distinguish drug-induced versus congenital long-QT syndrome and identify which ion channels are responsible for each.

6.2.2.2. Pharmacodynamics

1. Classify antiarrhythmic drugs according to the modernized classification inspired by the Vaughan-Williams framework recognizing the limitations of this classification system.
2. Explain the molecular mechanism of action of each drug in each drug class.
3. Relate the electrophysiologic actions of antiarrhythmic drugs in normal and abnormal myocardial and conduction tissue and their effects on the phases of the cardiac action potential.
4. Describe the alteration of slow (calcium-dependent) and fast (sodium-dependent) responses by antiarrhythmic drugs and how that relates to the use of specific agents in arrhythmias of different origins (ventricular vs. supraventricular).
5. Discriminate the relevant extracardiac actions of antiarrhythmic drugs with special reference to the actions of amiodarone.
6. Predict the major indirect autonomic actions of these drugs.

6.2.2.3. Pharmacokinetics

1. Relate the routes of administration, biotransformation, and excretion of drugs used in the management of arrhythmias.
2. Describe the onset and duration of action of drugs used in the management of arrhythmias.
3. Predict the impact of reduced cardiac output (due to myocardial infarction and cardiomyopathy) on pharmacokinetics (including half-life) and pharmacodynamics.
4. Predict how organ dysfunction from aging or other causes can affect the metabolism and elimination of drugs used in treating arrhythmias.
5. Relate the significance of electrolyte and acid-base imbalance in arrhythmia generation and their influence on antiarrhythmic drug action.

6.2.2.4. Adverse effects, drug interactions and contraindications

1. Anticipate the cardiac and extracardiac manifestations of toxicity from drugs used in the management of arrhythmias.
2. Anticipate beneficial and adverse interactions among drugs used in the management of arrhythmias.
3. Predict the possible contraindications of antiarrhythmic drugs in the presence of heart block or congestive heart failure and the precautions and contraindications in other conditions.
4. Recognize the classes of drugs (both antiarrhythmic and non-antiarrhythmic) that can produce acquired Long QT Syndrome (LQTS).

6.2.2.5. Therapeutic uses

1. Differentiate the treatment goals of rate control and rhythm control strategies in the management of supraventricular arrhythmias and identify drug classes used in each of these strategies.
2. Differentiate the role of the drugs used in the management of ventricular arrhythmias according to the most up to date guidelines.
3. Recognize the nonpharmacological approaches in management of arrhythmias.

6.2.2.6. Clinical Pharmacology

1. The Cardiac Arrhythmias Suppression Trial (CAST) study has changed our understanding of the risk of using sodium channel blockers post myocardial infarction in the management of cardiac arrhythmias. The use of antiarrhythmic drugs is being impacted considerably by data arising from studies of the pharmacogenomics of inherited channelopathies of ion transporters. In addition to long QT syndrome, there is now an appreciation of the existence of a short QT syndrome that is associated with atrial fibrillation and sudden death. Both phenotypes predispose an affected individual to cardiac arrhythmias, and can be induced by drug therapy for other disease states. Quinidine has provided benefit in lengthening the QT interval in the short QT syndrome. Disopyramide may also be effective in this pathological state. Currently, beta-adrenoceptor blocking drugs are considered to be the treatment of choice for long QT syndrome.
2. An update to Vaughan Williams classification has been proposed. Lei M, Wu L, Terrar DA, Huang CLH: Modernized classification of cardiac antiarrhythmic drugs. *Circulation* 138(17):1879–1896, 2018. doi: 10.1161/CIRCULATIONAHA.118.035455
3. 2018 ACC/AHA/HRS Guideline on the Evaluation and Management of Patients With Bradycardia and Cardiac Conduction Delay: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society.

Notes

1. Content recommendations for Calcium-Channel Blockers are covered under "*Management of Hypertension* (6.4)."

Content recommendations for β-Adrenoceptor Antagonist Agents are covered under "*Autonomic Nervous System* (3)*."*

6.3. Drugs Used for the Management of Acute and Chronic Heart Failure			
Recommended Curriculum Equivalent: 2.0 hr			
6.3.1. Drug Classes and Drugs			
Drugs affecting the renin-angiotensin aldosterone system			
ACE Inhibitors	**Angiotensin Receptor Blockers**	**Aldosterone Antagonists**	**Angiotensin Receptor-Neprilysin Inhibitor (ARNI)**
CAPTOPRIL ENALAPRIL LISINOPRIL	VALSARTAN Candesartan	SPIRONOLACTONE EPLERENONE	Sacubitril-valsartan
Sympathetic Agents		**PDE Inhibitors**	**Cardiac glycosides**
Beta blockers	**Beta agonists**		
CARVEDILOL METOPROLOL	DOBUTAMINE Dopamine	Milrinone	DIGOXIN

Diuretics	**Vasodilators**	**Other Drugs Used**
FUROSEMIDE HYDROCHLOROTHIAZIDE CHLORTHALIDONE Amiloride	NITROGLYCERIN Isosorbide dinitrate-hydralazine Nitroprusside	DAPAGLIFLOZIN Ivabradine

6.3.2. Content Recommendations for Management of Heart Failure

6.3.2.1. Physiology and pathophysiology: Introduction to cardiac inotropism

1. Illustrate the inotropic, dromotropic, chronotropic, and lusitropic effects of catecholamines as they relate to normal and abnormal cardiac function.
2. Compare and contrast the goals and principles for the management of acute and chronic heart failure.
3. Identify the most prevalent causes of heart failure and discuss treatment strategies to prevent the onset of heart failure.
4. Illustrate the basic pathophysiology of heart failure and the cardiac and extracardiac compensatory mechanisms that are activated.
5. Explain the role of genetics in the pathophysiology of heart failure and in the regulation of responsiveness to agents used in heart failure.

6.3.2.2. Pharmacodynamics

1. Explain the mechanisms of action of drugs used in the management of heart failure.
2. Explain the cardiovascular actions of drugs in the context of heart failure, including heart rate, contractility, peripheral vascular resistance, preload, afterload, cardiac remodeling, and coronary perfusion.
3. Summarize the extracardiac actions of drugs used in the management of heart failure, including renal perfusion.

6.3.2.3. Pharmacokinetics

1. Review the concept of loading dose and maintenance therapy and show the "plateau principle" regarding maintenance therapy without a loading dose in the management of acute heart failure.
2. Describe the routes of administration, biotransformation, and excretion of commonly prescribed drugs used in the management of heart failure.
3. Explain how aging affects the pharmacokinetics of commonly used drugs used in the management of heart failure.

6.3.2.4. Adverse effects, drug interactions and contraindications

1. Summarize the cardiac and extracardiac side effects and limitations of the drugs used for the management of heart failure.
2. Explain the significance of changes in serum electrolyte levels (potassium, sodium, calcium, magnesium) regarding drugs used in the management of heart failure (e.g.,digoxin, ACEi).
3. Predict the potential drug-drug interactions of medications used in the management of heart failure (e.g., both potassium-sparing and potassium depleting) as well as diseases (e.g., hypothyroidism) that may alter the management of heart failure.

6.3.2.5. Therapeutic uses

1. Differentiate the roles of drugs used in the management of acute and chronic heart failure according to the most current guidelines.
2. Describe the uses and limitations of digoxin in congestive heart failure and in atrial arrhythmias.

6.3.2.6. Clinical Pharmacology

Heidenreich PA, Bozkurt B, Aguilar D, Allen LA, Byun JJ, Colvin MM, et al. 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Circulation. 2022;145(18):e895-e1032

Notes

1. Objectives for Renin-angiotensin aldosterone agents are covered under vasoactive peptides.
2. Objectives for Sympathetic nervous system drugs are covered under the Autonomic Nervous System (3).
3. Objectives for diuretics are covered under Diuretics (7).

6.4. Drugs Used for the Management of Hypertension

Recommended Curriculum Equivalent: 4.0 hr

6.4.1. Drug Classes and Drugs

Drugs affecting the renin-angiotensin aldosterone system			
ACE Inhibitors	**Angiotensin Receptor Blockers**	**Renin Inhibitor**	
ENALAPRIL CAPTOPRIL LISINOPRIL	LOSARTAN VALSARTAN Candesartan Olmesartan	Aliskiren	

Sympathetic Antagonist Agents				
Alpha		**Beta**		**Mixed α and β**
Non-selective	α_1 Selective	Nonselective	β_1 Selective	
Phenoxybenzamine Phentolamine	PRAZOSIN Doxazosin	PROPRANOLOL Pindolol	METOPROLOL Atenolol Nebivolol	CARVEDILOL LABETALOL

Diuretics	**Vasodilators**		
CHLORTHALIDONE HYDROCHLOROTHIAZIDE Spironolactone Amiloride Furosemide Eplerenone	**Venous**	**Arterial**	**Both**
	ISOSORBIDE DINITRATE Nitroglycerin	HYDRALAZINE Minoxidil AMLODIPINE Nicardipine Verapamil Diltiazem	NITROPRUSSIDE

Centrally Acting Agents	**Hypertensive Emergency and Urgency**
CLONIDINE Methyldopa	NITROPRUSSIDE Fenoldopam Nicardipine Esmolol Clevidipine Nitroglycerin Labetalol

6.4.2. Content Recommendations

6.4.2.1. Physiology and pathophysiology: Introduction to the Vascular System and its Regulation

1. Review the determinants of systemic arterial blood pressure including the role of the autonomic nervous system, the regulation of fluid volume, and the renin-angiotensin aldosterone system.
2. Describe the role of the central nervous system in the regulation of blood pressure.
3. Discuss the role of vascular endothelium and locally released regulators of vascular tone in the maintenance of blood pressure.
4. List the types of hypertension and the relative prevalence of each.
5. Describe the current views for the etiology of primary hypertension.

6.4.2.2. Pharmacodynamics

1. Relate the mechanisms of drugs used in the management of hypertension to the tissue or organ systems important for the regulation of blood pressure.
2. Specify the mechanisms by which the drugs used in the management of hypertension exert their therapeutic effects.
3. Summarize the consequences of untreated hypertension and the beneficial effects achieved by therapeutic management of the disease.

6.4.2.3. Pharmacokinetics

1. Describe the time-course of antihypertensive activity (onset and duration of action) for commonly prescribed drugs.

6.4.2.4. Adverse effects, drug interactions and contraindications

1. Summarize the cardiac and extracardiac adverse effects of drugs used in the management of hypertension, including physiological reflex responses.
2. Provide examples and discuss the benefits and adverse effects of combination therapy in the management of hypertension.
3. Predict adverse interactions among drugs used in the management of hypertension and drugs that can alter physiological blood pressure regulation, including non-prescription medications (e.g., pseudoephedrine, NSAIDs, and herbal stimulants).

6.4.2.5. Therapeutic uses

1. Discuss the roles of evidence-based nonpharmacologic interventions for prevention and management of hypertension.
2. Summarize the algorithm for management of hypertension according to most up-to-date guidelines for the prevention, detection, evaluation, and management of high blood pressure in adults.
3. Specify the common pharmacologic therapies for chronic hypertension during pregnancy, secondary hypertension, and/or hypertensive emergencies.
4. Specify, according to the most up-to-date guidelines, the considerations for management of hypertension and other population subgroups (special populations that are resistant to treatment, patients with diabetes, isolated systolic hypertension esp. in elderly or renal failure).

6.4.2.6. Clinical Pharmacology

1. According to the most-up-to date guidelines (2017), the Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines, a systolic blood pressure between **120-129 mm Hg** and diastolic blood pressure **< 80 mm Hg** is considered elevated. **Stage 1 hypertension** is defined as a systolic blood pressure between **130-139 mm Hg** or diastolic blood pressure between **80-89 mm Hg**. S**tage 2 hypertension** is defined as a systolic blood pressure **≥ 140 mm Hg** or diastolic blood pressure **≥ 90 mm Hg**. If a patient has stage 1 hypertension and the 10-year risk of atherosclerotic cardiovascular disease is greater than 10% or the patient has cardiovascular disease, diabetes mellitus, or chronic kidney disease, lifestyle changes **combined with monotherapy** (thiazide-type diuretic, ACE inhibitor, angiotensin receptor blocker, DHP-calcium channel blocker; combination therapy can be an option) are recommended. Two or more antihypertensive medications are recommended for adult patients with stage 2 hypertension. The 2017 guidelines also recommend two or more antihypertensive medications for Black adult patients with hypertension to achieve a target blood pressure of less than **130/80 mm Hg**. Furthermore, the 2017 guidelines recommend a thiazide-type diuretic or calcium channel blocker for black adults with hypertension but without HF or CKD.

2. Whelton PK, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/ PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation. 2018 Oct 23;138(17): e484-e594.

Notes

1. Objectives for renin-angiotensin aldosterone agents are covered under Vasoactive Peptides.
2. Objectives for sympathetic nervous system drugs are covered under the Autonomic Nervous System (3). Objectives for diuretics are covered under Diuretics (7).

6.5. Drugs Used for the Management of Angina and Coronary Artery Disease

Recommended Curriculum Equivalent: 1.0 hr

6.5.1. Drug Classes and Drugs

Beta Blockers	Calcium Channel Blockers	Organic Nitrates	Metabolic Modulators	Cardiac Rate Control
ATENOLOL METOPROLOL PROPRANOLOL	DILTIAZEM VERAPAMIL Amlodipine Nifedipine	NITROGLYCERIN ISOSORBIDE MONONITRATE Isosorbide dinitrate	Ranolazine	Ivabradine

6.5.2. Content Recommendations

6.5.2.1. Introduction to Coronary Blood Flow and its Regulation

1. Relate the normal regulation of coronary blood flow to the events of the cardiac cycle.
2. Differentiate between the mechanism of myocardial oxygen supply and myocardial oxygen demand.
3. Differentiate the pathophysiology of classic (stable, exertional, exercise-induced, coronary artery disease), variant (Prinzmetal, vasospastic), and unstable angina (acute coronary syndrome).
4. Explain the significance of atherosclerotic coronary artery disease and coronary artery spasm (Prinzmetal angina) in the production of myocardial ischemia and angina pectoris.

6.5.2.2. Pharmacodynamics

1. Differentiate the principal therapeutic goals for the management of coronary artery disease from acute coronary syndrome.
2. Compare and contrast the mechanisms of action of drugs used in the management of coronary artery disease.
3. Relate the resulting vascular and cardiac actions of drugs to the principal therapeutic goals in the management of coronary artery disease including changes to parameters that determine myocardial oxygen supply and demand.

6.5.2.3. Pharmacokinetics

1. Describe the significance of routes of administration on onset and duration of action for drugs used in the management of coronary artery disease.
2. Explain the significance of "first-pass effect" and biotransformation on bioavailability for drugs used in the management of coronary artery disease.
3. Explain the causes of nitrate tolerance and the dosing strategies to minimize tolerance.

6.5.2.4. Adverse effects, drug interactions and contraindications

1. Predict the physiologic consequences and describe special adverse effects from the use of drugs in the management of coronary artery disease.
2. Identify clinical situations where drugs used in the management of coronary artery disease are contraindicated (e.g., use with a concurrent PDE5 inhibitor, negative chronotrope, inotrope, or dromotrope).

6.5.2.5. Therapeutic uses

1. Differentiate the use of drugs used for the management of angina (classic and vasospastic) according to the most up to date guidelines.
2. Describe the concept of "myocardial preservation" and discuss the use of drugs used to manage angina in the context of acute myocardial infarction with particular emphasis on adrenergic receptor antagonists.

6.5.2.6. Clinical Pharmacology

1. Nitroglycerin remains the initial treatment of choice for acute anginal attacks. Patients must be reminded that exposure to moisture will destroy a sublingual tablet formulation and potentially be misinterpreted as worsening of the disease. For chronic angina, long-acting nitrates are a reasonable next step, but tolerance is a problem when the drug is used at evenly spaced time intervals over 24 hours.
2. For chronic stable angina, beta-adrenergic receptor blocking drugs remain a reasonable choice with calcium channel blocking drugs as a secondary choice. Calcium channel-blocking drugs are preferred for vasospasm-induced angina, but the long-acting formulations are indicated as an appropriate treatment.

Notes

Objectives for sympathetic nervous system drugs are covered under the Autonomic Nervous System (3).

6.6. Drugs Used for the Management of Dyslipidemias

Recommended Curriculum Equivalent: 1.0 hr

6.6.1. Drug Classes and Drugs

BILE ACID SEQUESTRANTS	FIBRIC ACID DERIVATIVES	HMG CoA REDUCTASE INHIBITORS	OTHERS
CHOLESTYRAMINE	GEMFIBROZIL	ATORVASTATIN ROSUVASTATIN Pravastatin Simvastatin	Niacin Ezetimibe Lomitapide Evolocumab Icosapent ethyl Bempedoic acid Inclisiran

6.6.2. Content Recommendations

6.6.2.1. Physiology and Pathophysiology: Lipid Interactions with the Cardiovascular System

1. Differentiate the processes of lipoprotein (e.g., cholesterol, triglyceride) metabolism by intestinal and hepatic cells.
2. Summarize the basic pathophysiology and identify the etiology of atherosclerotic vascular disease and its relationship to the dyslipidemias.
3. Discuss the different types of dyslipidemias using the Frederickson classification system.

6.6.2.2. Pharmacodynamics

1. Compare the mechanisms of action of and predict the resultant lipoprotein level reduction from drugs used in the management of dyslipidemias.
2. Assess the advantages of appropriate drug combinations in the management of dyslipidemias.
3. Describe the relevant actions of these drugs, other than on lipid metabolism (e.g., pleiotropic effects).

6.6.2.3. Pharmacokinetics

1. Differentiate the duration of action and metabolism of statins and how this impacts clinical management and efficacy.

6.6.2.4. Adverse effects, drug interactions and contraindications

1. Predict the major adverse effects of drugs used in the management of dyslipidemias and coronary artery disease with special reference to the muscle and liver toxicities
2. Predict the drug-drug interactions that can interfere with absorption of digoxin or warfarin, exacerbate myopathy, or interfere with the metabolism of other relevant drugs.

6.6.2.5. Therapeutic uses

1. Describe according to the most up to date guidelines the management of dyslipidemias.
2. Specify the non-pharmacological management of dyslipidemias (i.e., lifestyle modifications and natural remedies that may benefit patients).
3. Specify the use of these agents in familial and acquired dyslipidemias, and their efficacy in atherosclerotic vascular disease.

6.6.2.6. Clinical Pharmacology

1. The statin class of drugs has become the de facto primary choice for treatment of hyperlipidemias. Choice of agent is often based on potential drug interactions, since their bioavailability is very low. Accumulation may be problematic with inhibition of first-pass elimination mechanisms. It is still controversial as to whether or not use of this drug class in elderly patients has an acceptable risk:benefit ratio.
2. Refer to important multicenter clinical trial data documenting efficacy in multiple patient groups.

3. The apparent lack of a threshold effect (lower is always better, even in the normal range of LDL).
4. HMG CoA reductase inhibitors can prevent acute coronary events and stroke and can be possible adjuncts for dementia and other pathological disorders. Consider the potential anti-inflammatory effects of "statins" on other disease states.
5. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines Grundy et al. Originally published10 Nov 2018 https://doi.org/10.1161/CIR.0000000000000625 Circulation. 2019;139:e1082–e1143.

Notes

1. Objectives for nicotinic acid (niacin) are also found under Vitamins (14).
2. Discuss drug-induced alterations in plasma lipids (e.g., protease inhibitor-induced hyperlipidemia; estrogen-induced hypolipidemia).
3. Review the role of thyroid hormone in affecting serum lipids and the findings in hyper- and hypothyroidism.

6.7. Drugs Used for the Management of ST-Elevation Myocardial Infarction (STEMI)/Myocardial Infarction/Acute Coronary Syndrome and Chronic Treatment of Cardiovascular Diseases including Atrial Fibrillation

Recommended Curriculum Equivalent: 1 hr

6.7.1. Drug Classes and Drugs

A. ANTIPLATELET AGENTS

ADP Receptor Antagonists	Glycoprotein IIb/IIIA Receptor Antagonists	Others
CLOPIDOGREL PRASUGREL Ticagrelor Ticlopidine	Eptifibatide Tirofiban	ASPIRIN Dipyridamole Cilostazol Vorapaxar (PAR-1 antagonist)

B. ANTICOAGULANTS

Heparins	Coumarins	Thrombin Inhibitors	Factor Xa Inhibitors
HEPARIN Enoxaparin	WARFARIN	DABIGATRAN (oral) Argatroban Bivalirudin	Fondaparinux Rivaroxaban (oral)

C. FIBRINOLYTICS

ALTEPLASE
Tenecteplase
Reteplase
Urokinase (Historical)
Streptokinase (Historical)

D. Antidotes

Protamine sulfate
Vitamin K
Fresh Frozen plasma
Aminocaproic acid
Idarucizumab
andexanet alpha

6.7.2. Content Recommendations

6.7.2.1. Hemostasis and Pathophysiology

1. Describe the four stages of hemostasis and the processes of dissolution.
2. Relate the concept of atherosclerotic plaque stability to complications in thrombotic disorders.
3. Classify red and white thrombi and identify thrombotic disorders where each type is dominant.

6.7.2.2. Pharmacodynamics

1. Compare and contrast the mechanisms of action of antiplatelet drugs, anticoagulants, and thrombolytics.
2. Relate the mechanisms of action of antiplatelet drugs, anticoagulants, and thrombolytics to the stages of hemostasis or processes of dissolution where they apply.
3. Predict the effectiveness of antiplatelet drugs or anticoagulants based on the predominant thrombi type found in thrombotic disorders.
4. Describe the mechanisms of drugs used in the event of anticoagulant or thrombolytic overdose or associated complication.

6.7.2.3. Pharmacokinetics

1. Compare and contrast the routes of administration of antiplatelet drugs and anticoagulants.
2. Discuss the route and timing of administration of thrombolytics.

6.7.2.4. Adverse effects, drug interactions and contraindications

1. Compare and contrast the adverse effects and drug interactions of anticoagulants and antiplatelets.
2. Describe contraindications with the use of antiplatelet drugs, anticoagulants, and thrombolytics.
3. Discuss concurrent use non-pharmacological agents (nutritional supplements, herbal agents, foods, diet rich in Vitamin K) which can interfere with effective blood coagulation.

6.7.2.5. Therapeutic uses

1. Interpret relevant laboratory findings (with the appropriate monitoring) of antiplatelet drugs and anticoagulants for therapeutic efficacy.
2. Differentiate the role of the drugs used in the management of ACS according to the most up-to-date guidelines according to the AHA ACLS Acute Coronary Syndrome Algorithm.
3. Differentiate the management and prophylaxis of thrombotic disorders (stroke, pulmonary embolism, deep vein thrombosis, and others) according to most up-to-date guidelines.
4. Discuss the management of complications or overdose of anticoagulants and thrombolytics.

6.7.2.6. Clinical Pharmacology

1. The use of the teaching mnemonic MONA (**M**orphine, **O**xygen, **N**itroglycerin, and **A**spirin) for management of ACS is no longer recommended as morphine and oxygen may be associated with higher mortality. (*de Alencar Neto J (January 25, 2018) Morphine, Oxygen, Nitrates, and Mortality Reducing Pharmacological Treatment for Acute Coronary Syndrome: An Evidence-based Review. Cureus 10(1): e2114. DOI 10.7759/cureus.2114*).
2. AHA ACL Acute Coronary Syndrome Algorithm guidelines are updated every 5 years, last updated in the 2020 American Heart Association Guidelines for CPR and ECC.
3. O'Gara P, Kushner F, Ascheim D, et al. 2013 ACCF/AHA Guideline for the Management of ST-Elevation Myocardial Infarction. J Am Coll Cardiol. 2013 Jan, 61 (4) e78–e140.https://doi.org/10.1016/j.jacc.2012.11.019
4. Many new agents are rapidly reaching the market to treat STEMI. Therapy with low dose aspirin plus clopidogrel appears to have reasonable evidence for efficacy. Alternatively, low molecular weight heparin therapy with addition of a glycoprotein IIb/IIIa receptor antagonist is also considered acceptable. There is increasing evidence that low molecular weight heparins are more effective and safer than the previously used standard intervention with unfractionated heparin. Use of combination endpoints to assess safety and efficacy of alternative drug treatments has clouded the ability to compare alternative strategies. In the management of atrial fibrillation, warfarin is still widely used, in spite of difficulties with control of INR. Newer oral anticoagulants are slowly replacing traditional drugs used for management of certain thrombotic disorders.

Notes

See Section I Drugs Acting on the Blood and Blood-forming Organs for Objectives on Thrombolytics, Anticoagulants and Antithrombotic Drugs (12).

The hope that pharmacogenetic diagnostic tools would resolve this problem has provided only a modest incremental improvement in the safety and efficacy of using warfarin as a drug intervention.

7. RENAL PHARMACOLOGY

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7.1 Diuretics

Introduction

Recommended Curriculum Equivalent: 2 hrs

7.1.1 Drug Classes and Drugs

Carbonic Anhydrase Inhibitor	Osmotic Diuretic	SGLT2 Inhibitors	Loop Diuretics
ACETAZOLAMIDE brinzolamide	mannitol	CANAGLIFLOZIN dapagliflozin empagliflozin	FUROSEMIDE torsemide ethacrynic acid

Thiazide Diuretics	K-sparing Diuretics	
	Aldosterone Antagonists	Na+ channel Blockers
HYDROCHLOROTHIAZIDE chlorthalidone metolazone	SPIRONOLACTONE eplerenone	AMILORIDE

7.1.2 Content Recommendations

7.1.2.1 Physiology and Pathophysiology

- Describe the location and function of major ion transporters and channels on renal epithelial membranes.
- Explain how sodium transport influences the reabsorption of other ions and water in the kidney.
- Explain how intrinsic renal disease or extrinsically/hormonally-altered renal function can cause hypertension, or edema

7.1.2.2 Mechanism of Action

- Describe the changes that occur with electrolyte transport, water reabsorption and hemodynamics when specific diuretics inhibit kidney function. Identify the transporter processes targeted by the various classes of diuretics.

7.1.2.3 Actions on organ systems

- Describe the relative magnitude and direction of changes that occur in sodium, potassium, bicarbonate and water excretion and hemodynamics when specific diuretics inhibit kidney function. Compare and contrast the effects of loop diuretics and thiazide diuretics on calcium and magnesium excretion.
- Describe the potential extra-renal consequences of diuretic-induced alterations in fluid and electrolyte homeostasis.
- Explain why SGLT2 inhibitors cause an osmotic diuresis when used clinically.

7.1.2.4 Pharmacokinetics

- Explain the importance of the organic anion transporters and protein binding to the renal action of diuretics.

- Contrast the pharmacokinetics of aldosterone antagonists with other diuretics.
- Provide examples of how organ dysfunctions can interfere with the effects of diuretics.

7.1.2.5 Adverse effects, drug interactions and contraindications

- Explain how thiazides and loop diuretics can cause a metabolic alkalosis
- Explain how diuretic therapy can lead to hyponatremia and hypo- or hyperkalemia.
- Describe the metabolic imbalances with diuretic therapy on glucose, urate, lipids, calcium, and magnesium. Explain the underlying mechanisms involved.
- Describe the clinical consequences of interactions between diuretics and drugs such as lithium, cardiac glycosides, oral hypoglycemic agents, uricosurics, antibiotics that cause renal toxicity, NSAIDs and inhibitors of renin-angiotensin-system.
- Describe why reduced renal perfusion can limit the use of thiazide diuretics.
- Contrast the unique adverse effects of specific diuretics.

7.1.2.6 Therapeutic uses

- Explain the renal and extra-renal mechanisms by which diuretics are useful in treating hypertension and edema due to heart, liver or kidney failure.
- Explain how osmotic drugs can reduce toxic nephropathy.
- Explain why diuretics are used to treat nephrogenic diabetes insipidus
- Explain the utility of diuretics for the treatment of primary aldosteronism and glaucoma.

7.1.2.7 Clinical Pharmacology

- Changes in tubule fluid pH can be used to increase the excretion of drugs by the kidneys.
- Hydrochlorothiazide can be used in a low dose to counteract the increase in circulating aldosterone secondary to use of an ACE inhibitor for the management of hypertension.
- Distal tubule diuretics such as thiazides spare calcium in patients with osteopenia and may also reduce the recurrence of calcium-containing kidney stones.
- Thiazide diuretics become ineffective in patients with a creatinine clearance less than 30 ml/min, necessitating a shift to oral loop diuretics that remain effective when the glomerular filtration rate is low.
- Potassium-sparing diuretics are relatively contraindicated in patients receiving ACE inhibitor therapy due to the increased likelihood of hyperkalemia, but are nevertheless cautiously used in combination when treating heart failure.
- Thiazide diuretics and loop diuretics other than ethacrynic acid are sulfonamides with immunological cross reactivity to other drugs in this class (e.g., sulfonylurea-containing antidiabetic drugs, sulfonamide-containing antimicrobial agents, celecoxib).

Notes

Objectives for diuretic use in cardiovascular diseases are covered under the Cardiovascular Section (6).
Objectives for renin-angiotensin-system modulating drugs are covered under the Cardiovascular Section (6) and Bioactive Peptides in the Autacoid Sectin (9).
Objectives for SGLT2 Inhibitors are covered under the Endocrine Section (11).
Objectives for drugs influencing plasma Ca2+ and PO_4^{3-} levels are covered under the Endocrine Section (11).
Objectives for drugs used in renal transplantation are covered under the Immunopharmacology Section (15).

7.2 Agents Affecting the Renal Conservation of Water

Recommended Curriculum Equivalent: 1 hr

7.2.1 Drug Classes and Drugs

Vasopressin Agonists	Vasopressin Antagonists
DESMOPRESSIN (V_2R) vasopressin ($V_1R > V_2R$)	conivaptan ($V_{1a}R$, V_2R) tolvaptan (V_2R)

7.2.2 Content Recommendations

7.2.2.1 Physiology and Pathophysiology

- Explain the mechanisms by which the kidney makes a concentrated or dilute urine
- Describe the roles of vasopressin, aquaporins, V_1 and V_2 receptors, cyclic AMP and prostaglandins in regulating renal epithelial water permeability.

7.2.2.2 Mechanisms of Action

- Describe how drugs can mimic or interfere with the cellular mechanisms of vasopressin.

7.2.2.3 Actions on organ systems

Compare and contrast the renal and extrarenal effects of vasopressin and desmopressin.

7.2.2.4 Pharmacokinetics

- Explain how altering the structure of vasopressin affects its pharmacokinetics and pharmacodynamics.

7.2.2.5 Adverse effects, drug interactions and contraindications

- Explain how NSAIDs can alter water reabsorption by the kidney.
- Explain how drugs such as lithium and NSAIDs can modify the action of vasopressin.
- Identify the clinical limitation for the use of tolvaptan.

7.2.2.6 Therapeutic uses

- Compare and contrast the therapy of central and nephrogenic diabetes insipidus.
- Describe the pharmacological treatment of the syndrome of inappropriate ADH secretion and the hypervolemic hyponatremia of heart failure.
- Describe the use of tolvaptan for the treatment for polycystic kidney disease.
- Describe the use of desmopressin for von Willebrand disease.

7.2.2.7 Clinical Pharmacology

- Vasopressin antagonists should be started or re-initiated in a hospital setting where the rate of hyponatremia correction can be carefully monitored as overly rapid correction has adverse effects (e.g., osmotic demyelination syndrome).
- Caution required during the use of conivaptan and tolvaptan concurrently with drugs inhibiting CYP3A or P-glycoprotein

Notes

Objectives for desmopressin-enhanced clotting factor release are covered under the Hemostasis and Blood Forming Drugs Section (12).

Similar objectives for vasopressin agonist and antagonists are covered under the Endocrine Section (11).

8. GASTROINTESTINAL PHARMACOLOGY
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<table>
<tr><th colspan="3">8.1 ACID REDUCERS: ANTIHISTAMINES & PROTEIN PUMP INHIBITORS</th></tr>
<tr><td rowspan="2">Endogenous substance or target</td><td colspan="2">H₂ Receptor Antagonists</td></tr>
<tr><td>First Generation</td><td>Second Generation</td></tr>
<tr><td>Histamine</td><td>CIMETIDINE</td><td>FAMODTINE
NIZATIDINE</td></tr>
<tr><td>Gastrointestinal H^+/K^+ ATPase</td><td colspan="2">Protein Pump Inhibitors (PPI)</td></tr>
<tr><td></td><td>Protein Pump Inhibitors (PPI)
OMEPRAZOLE
ESOMEPRAZOLE
Pantoprazole
Lansoprazole</td><td></td></tr>
<tr><th colspan="3">8.1.1 Content Recommendations</th></tr>
<tr><td colspan="3">8.1.1.1 Physiology and pathophysiology:
Describe the neurohumoral control of H^+ secretion by gastric parietal cells.
Describe the role of histamine in the different phases H^+ secretion.
Describe the causes of H^+ hypersecretion.
Explain the role of the H^+/K^+ ATPase protein pump in H+ production</td></tr>
<tr><td colspan="3">8.1.1.2 Mechanism of action:
Explain the molecular mechanism of action of the major categories of drugs described</td></tr>
<tr><td colspan="3">8.1.1.3 Actions on organ systems:
Describe the pharmacological effects of the drugs on the stomach.
Identify other organ systems that are affected by H_2-receptor antagonist administration.</td></tr>
<tr><td colspan="3">8.1.1.4 Pharmacokinetics:
Describe the pharmacokinetics of major and prototypical drugs identified.</td></tr>
<tr><td colspan="3">8.1.1.5 Adverse effects, drug interactions and contraindications:
Describe the principal adverse effects of H_2 receptor antagonists and PPIs.
Describe the clinically important drug interactions and principal contraindications.
Compare and contrast the adverse effects, drug interactions, and contraindications between first and second generation H2-receptor antagonists.</td></tr>
<tr><td colspan="3">8.1.1.6 Therapeutic uses:
Identify current therapeutic uses of H_2 receptor antagonists and PPIs.</td></tr>
<tr><td colspan="3">8.1.1.7 Clinical Pharmacology:
Identify which agents are approved for pediatric patients.</td></tr>
</table>

8.2 ACID REDUCERS: ACID NEUTRALIZERS		
Selected Antacids		
Endogenous substance	**Single agent**	**Mixed preparations**
H^+	CALCIUM CARBONATE MAGNESIUM HYDROXIDE ALUMINUM HYDROXIDE Sodium Bicarbonate Sodium Citrate	MAGNESIUM HYDROXIDE/ ALUMINUM HYDROXIDE BISMUTH SUBSALICYLATE
8.2.1 Content Recommendations		
8.2.1 1 Physiology and Pathophysiology: Describe the mechanisms of H^+ secretion in the stomach		
8.2.1.2 Mechanism of action: Describe the mechanism of action of antacid medications. Describe the differences in onset and duration of action of each antacid preparation.		
8.2.1.3 Actions on organ systems: Describe the pharmacological effects of the drugs in each class on the stomach.		
8.2.1.4 Pharmacokinetics: Describe the absorption and systemic actions of antacid preparations		
8.2.1.5 Adverse effects, drug interactions and contraindications: Describe the principal adverse effects of each antacid preparation. Describe the clinically important drug interactions with antacids. Describe the principal precautions and contraindications in the use of antacids.		
8.2.1.6 Therapeutic uses: Describe the primary indication of antacid use.		
8.2.1.7 Clinical Pharmacology: Identify concerns with antacid use in patients taking other medications		

8.3 OTHER DRUGS USED FOR THE TREATMENT OF PEPTIC ULCER DISEASE		
Cytoprotectant and antimicrobial agents		
Endogenous substance	**Endogenous Ligand Analog**	**Surface protectant**
PGE_2	MISOPROSTOL	SUCRALFATE
Targeted organism	**Antimicrobial**	**Misc antimicrobial effects**
Helicobacter pylori	**Antibiotic classes & drugs**	**Mixed properties**
	Macrolides: CLARITHROMYCIN ***Penicillins:*** AMOXICILLIN ***Fluoroquinolones:*** levofloxacin ***Tetracyclines:*** TETRACYCLINE, doxycycline ***Nitroimidazoles:*** METRONIDAZOLE, tinidazole	BISMUTH SUBSALICYLATE

8.3.1 Content Recommendations

8.3.1.1 Physiology and Pathophysiology:

Describe the mechanisms for production of the gastric cytoprotective barrier.

Describe medical and medication-induced causes of disruption of the cytoprotective barrier.

Describe the role of H. pylori in peptic ulcer disease.

Describe tests for evaluating H. pylori infection.

8.3.1.2 Mechanism of action:

Explain the mechanism of action of each drug with cytoprotective benefits

Describe the mechanisms of action for all agents involved in H. pylori eradication or other antimicrobial action.

8.3.1.3 Actions on organ systems:

Describe the pharmacological effect of each drug on the cytoprotective barrier.

Describe the effects of antimicrobials on normal GI flora and GI function.

8.3.1.4 Pharmacokinetics:

Describe the absorption, distribution metabolism and excretion of each drug.

8.3.1.5 Adverse effects, drug interactions and contraindications:

Describe the principal adverse effects of each drug.

Describe clinically important drug interactions of the drugs in each class.

Describe the principal contraindications of each agent.

8.3.1.6 Therapeutic uses:

Describe the primary indications for use of each drug.

Distinguish the agents used for triple, sequential, and quadruple therapy regimens for H. pylori eradication.

Describe ~~factors~~ the impact of macrolide resistance and penicillin allergy when selecting the best therapeutic options for a given patient.

Describe potential for antibiotic resistant strains of H. pylori.

8.3.1.7 Clinical Pharmacology:

Identify the Black box warnings for misoprostol.

Determine when testing should be performed for H. pylori diagnosis and eradication.

Notes: Antimicrobial agents are also covered in the Antimicrobial Section (16).

8.4 **PROKINETIC DRUGS AND LAXATIVES**

Drug Classes and Drugs

Drugs used to treat upper GI motility disorders	**Drugs used to treat lower GI motility disorders (Constipation)**	
ERYTHROMYCIN METOCLOPRAMIDE Domperidone *Antacids, proton pump inhibitors (PPIs), H2-receptor blockers are categorized in other sections*	**Prokinetic categories & drugs**	**Laxatives**
	Prostaglandin analogs LUBIPROSTONE ***Opioid antagonists*** NALOXEGOL METHYLNALTREXONE ALVIMOPAN ***Cholinomimetics*** Neostigmine Bethanechol ***Guanylate cyclase-C Agonist*** Linaclotide	***General laxatives*** DOCUSATE MAGNESIUM HYDROXIDE POLYETHYLENE GLYCOL SODIUM PHOSPHATE Bisacodyl ***Fiber-related products*** PSYLIUM METHYLCELLULOSE ***Natural OTC products*** Lactulose Castor oil Senna Cascara Mineral oil

8.4.1 Content Recommendations

8.4.1.1 Physiology and Pathophysiology:
Describe the neural and hormonal mechanisms controlling stomach and intestinal motility
Describe the changes in neural and hormonal control of stomach and intestinal motility that lead to delayed gastric emptying or accommodation.

8.4.1.2 Mechanisms of action:
Explain the molecular mechanism of action of each drug.

8.4.1.3 Actions on organ systems:
Describe why some drugs are selective for upper GI motility disorders and why others are selective for lower GI motility disorders.

8.4.1.4 Pharmacokinetics:
Describe the relevant pharmacokinetic features of each drug

8.4.1.5 Adverse effects, drug interactions and contraindications:
Describe the principal adverse effects of the drugs of each class.
Describe the clinically important drug interactions of the drugs of each class.
Describe the principal contraindications of the drugs of each class.

8.4.1.6 Therapeutic uses:
Outline the main therapeutic uses of the drugs of each class.

8.4.1.7 Clinical Pharmacology:
Designate how medications are useful in upper and/or lower GI disorders.
Discussion of adverse effects should include mention of CNS effects like EPS for the dopamine antagonists

8.5 **ANTI-DIARRHEAL DRUGS**

Drug Classes and Drugs

Opioid agonists	**Serotonergic antagonists**	**Alpha$_2$ Adrenergic agonists**	**Probiotics**
LOPERAMIDE Diphenoxylate	Alosetron Cilansetron	Clonidine Lofexadine	Bifidobacterium infantis Others *Note: not FDA approved*
Somatostatin Analog	**Muscarinic Antagonists**	**Misc antidiarrheal**	
Octreotide	ATROPINE DICYCLOMINE Hyoscyamine Scopolamine	BISMUTH SUBSALICYLATE Bismuth Citrate	

8.5.1 Content Recommendations

8.5.1.1 Physiology and Pathophysiology:

Describe the neural and hormonal mechanisms controlling colonic motility and water and electrolyte absorption and secretion.

Describe the conditions under which neural mechanisms controlling colonic motility and water and electrolyte absorption and secretion are impaired.

Describe the neural mechanisms of visceral sensation and visceral pain.

Describe the importance of maintaining normal gut flora and how disruption can lead to altered motility and absorption and secretion in the colon.

8.5.1.2 Mechanisms of action:

Explain the molecular mechanism of action of each drug in each drug class.

8.5.1.3 Actions on organ systems:

Describe the effects of each drug on gastrointestinal motility and colon activity,.

Explain actions on any other organ systems that relate to antidiarrheal properties

8.5.1.4 Pharmacokinetics:

Describe the absorption distribution metabolism and secretion of each drug.

8.5.1.5 Adverse effects, drug interactions and contraindications:

Describe the principal adverse effects of the drugs of each class.

Describe the clinically important drug interactions of the drugs of each class.

Describe the principal contraindications of the drugs of each class.

8.5.1.6 Therapeutic uses:

Identify the specific therapeutic applications of each class of drug.

Describe management of opioid withdrawal diarrhea.

Differentiate between use of agents in infectious diarrhea versus chronic diarrhea caused by irritable bowel syndrome, inflammatory bowel disorders, and medication-induced diarrhea.

8.6 DRUGS USED FOR THE TREATMENT OF INFLAMMATORY BOWEL DISEASE

8.6.1 Drug Classes and Drugs

Salicylates	Steroids	Anti-mitotic agents	Monoclonal antibodies
SULFASALAZINE 5-AMINO SALICYLIC ACID	BUDESONIDE PREDNISONE	Methotrexate 6-mercaptopurine Azathioprine Cyclosporine	INFLIXIMAB Adalimumab Certolizumab Vedolizumab Ustekinumab

8.6.2 Content Recommendations

8.6.1.1 Pathophysiology:
Compare and contrast the differences between ulcerative colitis and Crohn's disease.
Describe the mechanisms underlying the intestinal and extraintestinal symptoms of inflammatory bowel disease.
Explain the role of decreased microbial diversity to the pathophysiology of inflammatory bowel disease.

8.6.1.2 Mechanism of action:
Distinguish the mechanism of action of each drug class and how this underlies the reduction of the inflammatory symptoms of ulcerative colitis and Crohn's disease.

8.6.1.3 Actions on Organ Systems:

Identify organ-specific toxicities elicited by these agents.

8.6.1.4 Pharmacokinetics:
List the routes of administration of drugs in each class.
Described the absorption and distribution of each class of drug and how this impacts the choice of the route of administration.
Describe the mechanisms for bioactivation of the salicylates and how this impacts their use for the treatment of inflammatory bowel disease.

8.6.1.5 Adverse effects, drug interactions and contraindications:

List the major acute and chronic toxicities associated with each agent/class, and the cautious or prohibitive use of a drug class or specific agent.

Identify underlying disease states which would necessitate alternative therapy.

Describe the potential for the patient to develop/reactivate neoplasm or infectious diseases when treated with these agents.
Explain why patients treated with immunosuppressive agents for inflammatory bowel disease (IBD) are at increased risk of opportunistic infection or reactivation of latent infection.

Describe the clinically important drug interactions of the drugs of each class.
Identify agents contraindicated in pregnancy or in patients with other significant comorbidities.

8.6.1.6 Therapeutic uses:
Differentiate the use of each class of drug for the treatment of ulcerative colitis vs. Crohn's disease.
Identify other relevant approved indications.
Discuss the management of potential severe reactions resulting from treatment with these agents.

Notes:
Objectives for salicylates, and steroids, are also covered under the Autacoid Section (9).

Objectives for immunologic agents are also covered under the Immunopharmacology Section (15).

Objectives for antimitotic drugs are also covered under the Autacoid (9) and Cancer Pharmacology Sections (10).

8.7 EMETIC AND ANTI-EMETIC DRUGS

8.7.1 Drug Classes and Drugs

Emetic drugs

Dopamine receptor agonist	Non-selective emetics
Apomorphine	SYRUP OF IPECAC

Anti-Emetic Drugs

Dopamine receptor antagonists	5-HT_3 receptor antagonists	Cannabinoid receptor agonists	Histamine receptor antagonists
METOCLOPRAMIDE PROCHLORPERAZINE Haloperidol	DOLASETRON GRANISETRON ONDANSETRON PALONOSETRON Ramosetron	DRONABINOL Nabilone Marinol	DIMENHYDRINATE DIPHENHYDRAMINE Cyclizine Hydroxyzine Meclizine Promethazine
Neurokinin receptor antagonists	**Corticosteroids**	**Benzodiazepines**	**Muscarinic receptor antagonists**
APREPITANT	Dexamethasone PREDNISONE METHYL - PREDNISOLONE	LORAZEPAM DIAZEPAM Alprazolam	SCOPOLAMINE
		Herbal Agents GINGER	

8.7.2 Content Recommendations

8.7.2.1 Physiology and Pathophysiology:
Describe the underlying central and peripheral nervous system mechanisms mediating nausea and vomiting.
Explain how disturbances in the vestibular system can result in nausea and vomiting.
Explain how some drug classes induce nausea and vomiting when prescribed for other indications.

8.7.2.2 Mechanisms of action:
Describe the mechanism of action of emetic drugs.
Explain the mechanisms of action of each drug class used as an anti-emetic.
Describe the rationale for using anti-emetics with different underlying mechanisms in multi-drug nausea and vomiting treatment.

8.7.2.3 Actions on organ systems:
Describe the pharmacological effects of each drug on GI and other relevant organ systems.

8.7.2.4 Pharmacokinetics
Identify routes of administration and characterize benefits of using using specific routes relative to the patient's presenting condition(s).
Describe the absorption, distribution, metabolism and excretion of each drug class.
Explain how pharmacokinetic parameters can alter the onset and efficacy of anti-emetics.

8.7.2.5 Adverse effects, drug interactions and contraindications:
Describe the principal adverse effects of the drugs of each class.
Describe the clinically important drug interactions of the drugs of each class.
Identify adverse effects of special concern when antiemetics are used in special multitherapy circumstances, such as chemotherapy or post-operative recovery.
Identify the principal contraindications of the drugs of each class.

8.7.2.6 Therapeutic uses:
Identify appropriate indications for using emetic drugs.
Identify appropriate indications for using anti-emetic drugs.
Discuss the roles of anti-emetic drugs in reducing nausea and vomiting in special circumstances, including pregnancy, post-operative recovery, and chemotherapy .

8.7.2.7 Clinical Pharmacology:
Drugs listed as antiemetics are used to treat many other disorders.
Antiemetic drugs are often used as adjuvants in chemotherapy, migraines, and post-surgery recovery so it is critical to understand relevant drug interactions.

Notes:
Several drug classes are also covered in the CNS Section (4) which include benzodiazepines, dopamine receptor antagonists.
Muscarinic antagonists are covered in the Autonomic Section (3) and corticosteroids are covered in the Endocrine Section (11).

8.8 OTHER GASTROINTESTINAL DRUGS		
Anti-flatulent	**Pancreatic enzyme replacement**	**Gallstones Dissolution Agents**
SIMETHICONE Activated Charcoal	PANCRELIPASE	Ursodiol
Probiotics	**Chloride channel activators**	**Antibiotics for IBS**
Lactobacillus Bifidobacterium	LUBIPROSTONE	Rifaximin

8.8.1 Content Recommendations

8.8.1.1 Physiology and Pathophysiology
Explain the pathophysiological process underlying irritable bowel syndrome (IBS), flatulence, gallstones.

8.8.1.2 Mechanisms of action
Describe the mechanisms of action of each of the major classes of drugs.

8.8.1.3 Pharmacokinetics
Describe the route of administration, absorption, distribution, and elimination for drugs in each class.

8.8.1.4 Adverse effects, drug interactions and contraindications
Describe the principal adverse effects of the drugs of each class.
Identify the principal contraindications of the drugs of each class.

8.8.1.5 Therapeutic Use
Describe the therapeutic uses for agents in each drug category.

9. AUTACOIDS/NONSTEROIDAL ANTI-INFLAMMATORY/ASTHMATIC DRUGS

Subcommittee:
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<table>
<tr><th colspan="3">9.1 Histamine and Antagonists</th></tr>
<tr><td colspan="3">Recommended Curriculum Equivalent: 1.5 hr</td></tr>
<tr><th colspan="3">9.1.1 Drug Classes and Drugs</th></tr>
<tr><td colspan="3">H_1 Receptor Antagonists</td></tr>
<tr><td>First Generation</td><td colspan="2">Second Generation</td></tr>
<tr><td>DIMENHYDRINATE
DIPHENHYDRAMINE
PROMETHAZINE
chlorpheniramine
hydroxyzine</td><td colspan="2">FEXOFENADINE
LORATADINE
cetirizine</td></tr>
<tr><td>Endogenous Substances</td><td>H_2 Receptor Antagonists</td><td>Histamine Release Modifiers</td></tr>
<tr><td>HISTAMINE</td><td>CIMETIDINE
FAMOTIDINE
RANITIDINE
nizatidine</td><td>CROMOLYN
OMALIZUMAB</td></tr>
<tr><th colspan="3">9.2 Content Recommendations</th></tr>
<tr><td colspan="3">9.2.1 Physiology and pathophysiology
Describe the synthesis, storage, release and cellular sources of histamine.
Describe the metabolism and elimination of histamine.
Discuss the tissue distribution and function of the four major classes of histamine receptors (with emphasis on H1 and H2, but with mention of relevance of H3 and H4).</td></tr>
<tr><td colspan="3">9.2.3 Mechanism of action
Explain the molecular mechanism of action of each drug in each drug class.</td></tr>
<tr><td colspan="3">9.2.4 Actions on organ systems
Explain the pharmacological effects of the drugs in each class on various organ systems.
Distinguish the histamine receptor subtypes responsible for mediating the effects of histamine in each organ system.</td></tr>
<tr><td colspan="3">9.2.5 Pharmacokinetics
Describe the pharmacokinetics of the first-generation and second-generation antihistamines.</td></tr>
<tr><td colspan="3">9.2.6 Adverse effects, drug interactions and contraindications
Describe the principal adverse effects and contraindications of the drugs in each class.
Discuss the clinically important drug interactions of the drugs in each class.</td></tr>
<tr><td colspan="3">9.2.7 Therapeutic uses
Differentiate the use of the antihistamines in the management of allergy, sedation, and motion sickness.</td></tr>
</table>

9.2.8 Clinical Pharmacology

Dimenhydrinate and diphenhydramine have a relatively narrow therapeutic index.

The inhibition of CYP450 enzymes by cimetidine increases the potential for toxicity of concurrently ingested drugs metabolized by these enzymes.

9.2.9 Relevance

USMLE topic	**Principles of therapeutics**
Biology of Tissue Response to Disease Abnormal Processes-Management - obstructive airway disease, allergic rhinitis (Respiratory); peptic ulcer (GI);	Antihistamines, H2 antagonists, mast cell stabilizer
AAMC Medical School Objectives Project Report X **Patient Safety-**Table 1	**Topic C** Drug treatment of common conditions and disease

Notes

Objectives for H1-receptor antagonists are covered in the Pulmonary Pharmacology Section (5).
Objectives for H2-receptor antagonists are covered in the Gastrointestinal Pharmacology Section (8).
Use of H3 inverse agonists such as pitolisant in narcolepsy is covered in the CNS Section (4).
Objectives for Histamine Release Modifiers are covered in Asthma Drugs (Section 9.7).

9.3 5-Hydroxytryptamine (5-HT, Serotonin): Agonists & Antagonists

Recommended Curriculum Equivalent: 1.0 hr

9.3.1 Drug Classes and Drugs

Serotonin and Serotonin Receptor Agonists	Selective Serotonin Reuptake Inhibitors (SSRIs)	Serotonin Antagonists
SEROTONIN SUMATRIPTAN Zolmitriptan Dihydroergotamine	FLUOXETINE, SERTRALINE ESCITALOPRAM	ONDANSETRON CYPROHEPTADINE

9.3.2 Content Recommendations

9.3.2.1 Physiology and pathophysiology

Describe the pathways of serotonin synthesis, storage, metabolism and release.

Discuss the tissue distribution and function of the classes (and subclasses) of serotonin receptors with emphasis on 5HT1R, 5HT2R, and 5HT3R.

Identify the major types of serotonin receptors relevant to therapeutic drugs acting in the brain, the vasculature and the GI tract.

Describe the roles of serotonin in migraine, carcinoid syndrome, and CNS disorders (emesis; mood disorders and other psychiatric conditions are covered in CNS drugs).

9.3.2.2 Mechanism of action

Explain the molecular mechanism of action of each drug in each drug class.

9.3.2.3 Actions on organ systems

Describe the pharmacological effects of the drugs in each class on various organ systems.

9.3.2.4 Pharmacokinetics

Specify key pharmacokinetic parameters of agents within a drug class, including the route of administration, in relation to differential treatments and paradigms (i.e., abortive vs prophylactic).

9.3.2.5 Adverse effects, drug interactions and contraindications

Describe the principal adverse effects (including serotonin syndrome) and contraindications of the drugs in each class.

Discuss the clinically important drug interactions of the drugs in each class.

9.3.2.6 Therapeutic uses

Differentiate the use of these drugs in migraine (prophylaxis vs. abortive therapy), nausea and depressive and anxiety disorders.

Note the use of the cyproheptadine (a 5HT2A and H1 antagonist) in carcinoid and serotonin syndrome.

9.3.2.7 Clinical Pharmacology

NSAIDS or acetaminophen are often used for mild symptoms of migraine.

Sumatriptin is contraindicated in persons taking MAO inhibitors or within 24 hours of another 5-HT1 agonist or ergotamine derivatives.

Serotonin reuptake inhibitors are treatments for anxiety disorders and depression.

9.3.2.8 Relevance

USMLE topic	**Principles of therapeutics**
Central and Peripheral Nervous System- Normal processes: cell/tissue structure and function-synthesis, storage, release, reuptake, and degradation of neurotransmitters and neuromodulators Abnormal processes - management: CNS - migraine, mood disorders; GI - nausea	Mechanisms of action and use of drugs for treatment of migraines, mood disorders, and nausea

AAMC Medical School Objectives Project Report X Patient Safety-Table 1	**Topic C** Drug treatment of common conditions and disease

9.4 Nitric Oxide (NO) and Nitric Oxide-cGMP Signaling Drugs

Recommended Curriculum Equivalent: 0.5 hr

9.4.1 Drug Classes and Drugs

Agonist	PDE-5 inhibitor	NO Donors	PGE_1 Analog
NITRIC OXIDE	SILDENAFIL	SODIUM NITROPRUSSIDE NITROGLYCERIN	ALPROSTADIL

9.4.2 Content Recommendations

9.4.2.1 Physiological roles of NO and cGMP

Describe the mechanisms and cellular site of endogenous synthesis of nitric oxide (NO) and its interactions with guanylyl cyclase to regulate cellular levels of cGMP.

Explain the roles of NO and cGMP in local control of blood flow, erectile dysfunction and relaxation of the pulmonary vasculature.

9.4.2.2 Mechanism of action

Explain the molecular mechanism of action of NO, guanylyl cyclase and each drug in each class.

9.4.2.3 Actions on organ systems

Describe the pharmacological effects of the drugs in each class on various organ systems.

9.4.2.4 Pharmacokinetics

Specify the key pharmacokinetic parameters of agents within each drug class, including their effects on the constitutive and inducible synthesis of nitric oxide and on nitric oxide release.

9.4.2.5 Adverse effects, drug interactions and contraindications

Describe the principal adverse effects and contraindications of the drugs in each class.

Discuss the clinically important drug interactions of the drugs in each class.

9.4.2.6 Therapeutic uses

Differentiate the use of these drugs in cardiac and pulmonary disorders.

Explain the use of these drugs for the treatment of erectile dysfunction and benign prostatic hyperplasia (BPH).

9.4.2.7 Clinical Pharmacology

Simultaneous use of PDE inhibitors is contraindicated in patients taking nitrate preparations.

9.4.2.8 Relevance

USMLE topic General principles- signal transduction Abnormal process - management: Cardiovascular system Pulmonary system Male Reproductive System	**Principles of therapeutics** Mechanisms of action, use, and adverse effects of drugs for treatment of coronary artery disease, acute coronary syndrome, hypertension, pulmonary hypertension, erectile dysfunction, BPH
AAMC Medical School Objectives Project Report X **Patient Safety**-Table 1	**Topic C** Drug treatment of common conditions and disease

Notes

Objectives for NO donors are covered under Cardiac Drugs.

Objectives for drugs related to prostaglandins in ED are covered under Eicosanoids.

9.5 Eicosanoids: Agonists & Antagonists

Recommended Curriculum Equivalent: 1.0 hr

9.5.1 Drug Classes and Drugs

Prostanoids

Endogenous	Analogs	Cyclooxygenase (COX) Inhibitors
PGE_2 $PGF_{2\alpha}$ PROSTACYCLIN THROMBOXANE A_2	ALPROSTADIL MISOPROSTOL LATANOPROST EPOPROSTENOL	ASPIRIN IBUPROFEN NAPROXEN MELOXICAM CELECOXIB

Leukotrienes

Endogenous	Leukotriene Modifiers
LTB_4 LTC_4 LTD_4 LTE_4	MONTELUKAST Zafirlukast Zileuton

9.5.2 Content Recommendations

9.5.2.1 Physiology and Pathophysiology

Describe the synthesis of prostaglandins, thromboxanes, leukotrienes from arachidonic acid.

Explain physiologic and pathophysiologic roles of eicosanoids in regulation of local blood flow, airway resistance, inflammation and nociception.

9.5.2.2 Mechanism of action

Explain the molecular mechanism of action of each drug in each drug class.

9.5.2.3 Actions on organ systems

Describe the pharmacological effects of the drugs in each class on various organ systems.

Differentiate between drugs inhibiting leukotriene synthesis (zileuton) from leukotriene action at CysLT1 receptors (montelukast).

9.5.2.4 Pharmacokinetics

Describe the metabolism and elimination of eicosanoids

9.5.2.5 Adverse effects, drug interactions and contraindications

Describe the principal adverse effects and contraindications of the drugs in each class.

Discuss the clinically important drug interactions of the drugs in each class.

Describe the shunting of arachidonic acid metabolism to the production of leukotrienes by inhibition of COX enzymes, leading to bronchoconstriction.

9.5.2.6 Therapeutic uses

Describe the clinical utility of prostaglandin analogs and the inhibition of prostaglandin synthesis.

9.5.2.7 Clinical Pharmacology

The leukotriene modifiers remain secondary choices for the management of patients with asthma.

Prostaglandin analogs (such as misoprostol) are contraindicated in women who are pregnant or are likely to become pregnant.

Misoprostol is most often used together with an NSAID (most often diclofenac) to reduce the risk of a GI bleed in patients requiring chronic drug therapy with an anti-inflammatory analgesic.

9.5.2.8 Relevance	
USMLE topic General principles - Biology of tissue response to disease Abnormal process - management: CNS - glaucoma Pulmonary System - asthma GI- peptic ulcer	**Principles of therapeutics** Mechanisms of action and use of drugs for treatment of disorders of asthma, peptic ulcer disease, glaucoma, pain,
AAMC Medical School Objectives Project Report X Patient Safety-Table 1	**Topic D** Drug treatment of common conditions and diseases, using frequently prescribed classes of drugs for the treatment and prevention of disease
Notes Objectives for the Leukotriene Modifiers are covered in the Pulmonary Pharmacology (5) Section.	

9.6 Bioactive Peptides

Recommended Curriculum Equivalent: 0.5 hr

9.6.1 Drug Classes and Drugs

Kinins	Neuropeptides	
	Endogenous	Antagonists
BRADYKININ neurokinin	Substance P CGRP VIP Angiotensin II	APREPITANT rimegepant

9.6.2 Content Recommendations

9.6.2.1 Physiology and Pathophysiology:

Describe the synthesis and metabolism of kinins and the pathological factors that can trigger kinin formation.

Explain the roles of substance P, neurokinins and CGRP in pain perception and local inflammation as well as the probable role of substance P in emesis.

Describe briefly the receptors activated by substance P, bradykinin, and other neurokinins.

Describe the angiotensin II pathway and its role in regulation of blood pressure.

9.6.2.2 Therapeutic uses:

Describe the use of the neurokinin antagonist, aprepitant, as an antiemetic.

Describe the use of angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blocking agents (ARBs) in the treatment of hypertension and renal protection.

Explain the use of CGRP antagonists for migraine treatment.

9.6.2.3 Adverse effects, drug interactions and contraindications

List the principal adverse effects and contraindications of the drugs in each class.

Discuss the clinically important drug interactions of the drugs in each class.

Describe the effects of ACE inhibitors on the metabolism of bradykinin and the production of cough related to ACE inhibitor therapy.

9.6.2.4 Clinical Pharmacology

Where cough is induced by treatment with an ACE inhibitor, this side effect may be eliminated by substitution with an angiotensin receptor antagonist. Avoid concurrent use of an ACE inhibitor and an angiotensin receptor antagonist.

9.6.2.5 Relevance

USMLE topic	**Principles of therapeutics**
Biology of tissue response to disease CV - Cell structure and function (neural and hormonal regulation) Abnormal processes- management: Gastrointestinal System- nausea CNS - migraine	CV - regulation of heart, blood pressure, blood volume Mechanisms of action and use of drugs for treatment of nausea, migraine
AAMC Medical School Objectives Project Report X **Patient Safety**-Table 1	**Topic C** Drug treatment of common conditions and disease

9.7 Drugs used for treating Asthma and COPD

Recommended Curriculum Equivalent: 1 hr

9.7.1 Drug Classes and Drugs

Anti-inflammatory Drugs		Leukotriene Modifiers	
Glucocorticoids	Modulators of mast cell degranulation	Leukotriene receptor antagonists	5-LO inhibitor
BECLOMETHASONE FLUTICASONE	CROMOLYN omalizumab	MONTELUKAST Zafirlukast	zileuton

Bronchodilators			
β_2 Agonists		Methylxanthines	Muscarinic receptor antagonists
Short acting	Long acting		
ALBUTEROL terbutaline	SALMETEROL	THEOPHYLLINE aminophylline	IPRATROPIUM Tiotropium

9.7.2 Content Recommendations

9.7.2.1 Physiology and Pathophysiology

Describe the disease processes of asthma and COPD including airway inflammation, bronchial smooth muscle constriction, and mast cell degranulation.

Describe the role of various mediators (histamine, acetylcholine, proteases, leukotrienes C4, D4; prostaglandins; cytokines) in asthma and COPD.

9.7.2.2 Mechanisms of action

Explain the molecular mechanism of action of each drug in each drug class.

9.7.2.3 Actions on organ systems

Differentiate the effects on the lung of the quick relief drugs and the drugs used for long-term control.

9.7.2.4 Pharmacokinetics

Distinguish the appropriate routes of administration of each drug.

List the main drugs and clinical situations that can alter the pharmacokinetics of theophylline.

9.7.2.5 Adverse effects, drug interactions and contraindications

Describe the principal adverse effects, the clinically important drug interactions, and principal contraindications of the drugs of each class.

9.7.2.6 Therapeutic uses

Differentiate the use of these drugs in asthma (short term relief and long-term control) and their use in COPD.

9.7.2.7 Clinical Pharmacology

Long-acting beta-2 receptor agonists are generally used in combination with inhaled steroids.

There is no good evidence for superiority of any of the short-acting beta-2 receptor agonist congeners.

Tiotropium has supplanted ipratropium as an antimuscarinic bronchodilator strategy due to its more convenient once daily dosage recommendation but ipratropium is used for rhinitis and nasal allergies. Antimuscarinic and anti-leukotriene drug therapy remain useful in the management of asthma. Antimuscarinics are often preferred bronchodilators in the management of COPD.

9.7.2.8 Relevance

USMLE topic	**Principles of therapeutics**
Respiratory System	Mechanisms of action and use of drugs for treatment of disorders of the respiratory system-bronchodilator drugs

AAMC Medical School Objectives Project Report X **Patient Safety**-Table 1	**Topic C** Drug treatment of common conditions and disease
Notes Objectives for steroids are covered in the Endocrine Section (11). Objectives for drugs used for asthma and COPD are also found in Pulmonary Section (5).	

9.8 Hypersensitivity and Immunopharmacology

Recommended Curriculum Equivalent: 1 hr

9.8.1 Drug Classes and Drugs

Immunosuppressants

Cytotoxic drugs	Lymphotoxic drugs	Drugs acting on Immunocompetent cells	Drugs acting on cytokines or on cytokine receptors	Other
AZATHIOPRINE	PREDNISONE Antithymocyte immunoglobulin	CYCLOSPORINE TACROLIMUS MYCOPHENOLATE MOFETIL Muromonab Sirolimus	DACLIZUMAB INFLIXIMAB Etanercept	Rh_o(D) immune globulin Lenalidomide Thalidomide

Immunostimulants and colony stimulating factors

EPOETIN ALFA
FILGRASTIM (G-CSF)
INTERFERONS
SARGRAMOSTIM (GM-CSF)
ldesleukin
BCG vaccine

9.8.2 Content Recommendations

9.8.2.1 Physiology and Pathophysiology
Describe the role of immunoglobulins (IgE, IgG, IgM) and cytokines in the immune response.
Differentiate different types of allergic reactions (Type I-IV) and factors (e.g. cytokines, MHC) involved
Describe the release of allergic mediators and processes leading to hypersensitivity.

9.8.2.2 Mechanisms of action
Explain the molecular mechanism of action of each drug in each drug class.

9.8.2.3 Actions on organ systems
Relate the main effects of each drug to its molecular mechanism of action.

9.8.2.4 Pharmacokinetics
Describe the route of administration and the relevant pharmacokinetic features of each drug in each drug class.

9.8.2.5 Adverse effects, drug interactions and contraindications
Describe the principal adverse effects of the drugs of each class.
Describe the clinically important drug interactions of the drugs of each class.
Describe the principal contraindications of the drugs of each class.

9.8.2.6 Therapeutic uses
Outline the main therapeutic uses of the drugs of each class.

9.8.2.7 Clinical Pharmacology
These drugs are almost always used in combinations. Emphasize the increased risk of activation of latent infection and increased susceptibility to tuberculosis. Some of these drugs suspected to increase the risk of cancer.

9.8.2.8 Relevance

USMLE topic	**Principles of therapeutics**
Immune System	Mechanisms of action and use of drugs that specifically affect immune function-immunomodulating drugs

AAMC Medical School Objectives Project Report X **Patient Safety**-Table 1	**Topic C** Drug treatment of common conditions and disease
Notes Objectives for Corticosteroids are covered in the Endocrine Section (11).	

9.9 Analgesic, Antipyretic, Anti-inflammatory

Recommended Curriculum Equivalent: 1 hr

9.9.1 Drug Classes and Drugs

Nonsteroidal Anti-inflammatory Drugs (NSAIDS)

Salicylic acid Derivatives	Nonselective COX inhibitors	Selective COX-2 inhibitors
ACETYLSALICYLIC ACID mesalamine sodium salicylate	IBUPROFEN NAPROXEN diclofenac indomethacin ketorolac piroxicam sulindac	CELECOXIB

Analgesic, Antipyretic Drugs	Antidote for acetaminophen toxicity
ACETAMINOPHEN	Acetylcysteine

9.9.2 Content Recommendations

9.9.2.1 Physiology and Pathophysiology of pain, inflammation & hyperthermia

Outline the physiological basis of temperature control and peripheral sensory pain fibers.
Describe the role of eicosanoids and bradykinin in causing local pain, edema and fever.
Outline the pathophysiology of acute and chronic inflammation.

9.9.2.2 Mechanisms of action

Explain the molecular mechanism of action of each drug in each drug class.
Differentiate the mechanisms of action of acetylsalicylic acid, acetaminophen, and NSAIDS.

9.9.2.3 Actions on organ systems

Differentiate the effects on pain, fever, and inflammation of the drugs in each class.

9.9.2.4 Pharmacokinetics

Describe the metabolism of and mechanism of toxicity of acetaminophen.
Describe the dose-dependance of the elimination of acetylsalicylic acid.

9.9.2.5 Adverse effects, drug interactions and contraindications

Describe the principal adverse effects of the drugs of each class.
Describe consequences of protein binding, zero order metabolism, and irreversible inhibition related to acetylsalicylic acid.
Describe the clinically important drug interactions of the drugs of each class.
Describe the principal contraindications of the drugs of each class.

9.9.2.6 Therapeutic uses

Differentiate the use of these drugs in treatment of pain, fever, and inflammation.
Describe the principles of treatment for acetaminophen toxicity.
Describe the principles of treatment for salicylate toxicity.

9.9.2.7 Clinical Pharmacology

PGE2 causes release of bicarbonate in the stomach together with an ability to inhibit acid secretion. These effects help to protect the gastric epithelium for acid. Aspirin and NSAIDS by inhibiting PGE2 production, remove this protective mechanism leading to ulceration and GI bleeding.

NSAIDs can increase the risk of heart attack or stroke in patients with or without heart disease or risk factors for heart disease. The risk of myocardial infarction or stroke can occur as early as the first weeks of using an NSAID and may increase with longer use of the NSAID. There also is an increased risk of heart failure with NSAID use.

In some clinical conditions such as congestive cardiac failure, hepatic cirrhosis, chronic renal disease, renal blood flow is dependent on the vasodilator effect of the PGs. With NSAIDS or aspirin this beneficial effect is removed, and renal blood flow and GFR can fall. This can precipitate renal failure and cause edema.

Never use two NSAIDs concurrently. Naproxen is indicated in patients resistant to other propionic acid congeners because it is the only congener that is present in the pure active isomer. Resistance may include a component of inability to convert the inactive isomer to its active form, since this metabolic pathway is highly variable among patients.

Sulindac is a prodrug, converted to the active sulfide metabolite in tissues and by gut flora. It is reputed to be less toxic to the kidney than other NSAIDs, with less effect on local prostaglandin production (perhaps because of re-oxidation in the kidney to the inactive sulfoxide form). This relative "renal-sparing" action may allow use of sulindac, unlike other NSAIDs, in a patient with impaired renal function.

Indomethacin is no longer a first-line drug, due to its gastrointestinal toxicity.

Selective COX-2 inhibitor drugs have a slower onset of analgesia and should not be used for management of acute pain. Remember that COX-2 is the primary isoenzyme in the kidney and the brain. One should emphasize the danger when two highly-bound drugs are used together – e.g. most NSAIDs and sulfonylureas. Important also is the risk of bleeds with warfarin + an NSAID due to different mechanisms of anticoagulant effect.

9.9.2.8 Relevance

USMLE topic Musculoskeletal System	**Principles of therapeutics** Mechanisms of action and use of drugs for treatment of disorders of the musculoskeletal system-non-steroidal anti-inflammatory drugs and analgesics
AAMC Medical School Objectives Project Report X **Patient Safety**-Table I	**Topic D** Drug treatment of common conditions and diseases, using frequently prescribed classes of drugs for the treatment and prevention of disease

Notes:

Objectives for glucocorticoids are covered in the Endocrine Section (11).

Objectives for opiates are covered under CNS Section (4).

9.10 Antirheumatic Drugs

Recommended Curriculum Equivalent: 0.5 hr

9.10.1 Drug Classes and Drugs

COX Inhibitors	Corticosteroids	DMARDS (Disease Modifying Antirheumatic Drugs)	
		Biologics	Traditional
ASPIRIN IBUPROFEN NAPROXEN Celecoxib	Prednisone	ETANERCEPT INFLIXIMAB abatacept tocilizumab anakinra rituximab	METHOTREXATE hydroxychloroquine leflunomide sulfasalazine

9.10.2 Content Recommendations

9.10.2.1 Mechanism of action

Explain the molecular mechanism of action common to all nonsteroidal anti-inflammatory drugs (NSAIDs).
Explain the molecular mechanism of action of corticosteroids.
Describe the likely mechanisms of antirheumatic action of the DMARDS.

9.10.2.2 Pharmacokinetics

List the routes of administration of drugs in each class.
Recognize the time required before the onset of action of the DMARDS.

9.10.2.3 Adverse effects, drug interactions and contraindications

Describe the main adverse effects of the drugs of each class.
Describe the clinically important drug interactions of the drugs of each class.
Describe the principal contraindications or precautions of the drugs of each class.

9.10.2.4 Therapeutic uses

Outline the use of the NSAIDS, corticosteroids, and DMARDS in arthritic disorders.

9.10.2.5 Clinical Pharmacology

Biologic DMARDs increase susceptibility to infections including reactivation of tuberculosis.
Avoid combinations of abatacept, anakinra or tocilizumab with TNF inhibitors.

9.10.2.6 Relevance

USMLE topic Musculoskeletal System	**Principles of therapeutics** Mechanisms of action and use of drugs for treatment of disorders of the musculoskeletal system- antigout therapy and immunosuppressive drugs
AAMC Medical School Objectives Project Report X **Patient Safety**-Table 1	**Topic C** Drug treatment of common conditions and diseases, using frequently prescribed classes of drugs for the treatment and prevention of disease

Notes

Objectives for COX inhibitors are covered under Analgesic, Antipyretic, Anti-inflammatory Drugs.

9.11 Gout

Recommended Curriculum Equivalent: 0.5 hr

9.11.1 Drug Classes and Drugs

Drugs for the gouty attack	Decrease urate formation	Increase urate excretion
NSAIDs Colchicine	ALLOPURINOL Febuxostat Rasburicase	PROBENECID Sulfinpyrazone

9.11.2 Content Recommendations

9.11.2.1 Physiology and Pathophysiology
Describe the causes and pathophysiology of acute gouty arthritis and chronic tophaceous gout.

9.11.2.2 Mechanisms of action
Explain the molecular mechanism of action of each drug in each drug class.

9.11.2.3 Actions on organ systems
Describe the pharmacological effects of each drug in each class.
Differentiate the effects of the drugs in the treatment of gout.

9.11.2.4 Adverse effects, drug interactions and contraindications
Describe the principal adverse effects of the drugs of each class.
Describe the clinically important drug interactions of the drugs of each class
Describe the principal contraindications of the drugs of each class.
List the drugs that interfere with the renal excretion of uric acid.
Describe the mechanism of gouty flare-up associated with the treatment of chronic tophaceous gout.

9.11.2.5 Therapeutic uses
Differentiate the use of these drugs in the treatment of acute gout attacks and as prophylactic therapies.

9.11.2.6 Clinical Pharmacology
An NSAID is often the drug of choice for acute attacks with severe pain; different NSAIDS appear equally effective. Colchicine is effective but is slower to work than NSAIDS. Urate lowering drugs are recommended if the patient experiences 2 or more attacks per year. Allopurinol or febuxostat are the first line options with the uricosuric agents as second-line options. Anti-inflammatory prophylaxis (with colchicine or an NSAID) is recommended for all gout patients when urate-lowering therapy is started.

9.11.2.7 Relevance

USMLE topic Musculoskeletal System	**Principles of therapeutics** Mechanisms of action and use of drugs for treatment of disorders of the musculoskeletal system- antigout therapy and immunosuppressive drugs
AAMC Medical School Objectives Project Report X **Patient Safety**-Table 1	**Topic C** Drug treatment of common conditions and diseases, using frequently prescribed classes of drugs for the treatment and prevention of disease

Notes

9.12 Drugs for specific clinical entities					
Drugs for headaches					
9.12.1 Drug Classes and Drugs					
Acute or Abortive Treatment			Prophylaxis		
Analgesics	Triptans	Ergot alkaloids	β-Blockers	Antiepileptics	Others
Acetaminophen aspirin (NSAIDS)	sumatriptan	ergotamine	propranolol	valproate	Amitriptyl verapamil

9.12.1.1 Therapeutic uses

Outline the use of these drugs in the acute and prophylactic treatment of headaches including migraine, tensi and cluster headaches.

Outline the management of treatment of overdose to acetaminophen.

Drugs Used for Treating Alopecia	
9.12.2 Drug Classes and Drugs	
Alopecia Areata	Androgenetic Alopecia
cyclosporine glucocorticoids	Finasteride Minoxidil

Drugs Used for Treating HPV & Molluscum, Actinic Keratoses, BCC and SCC, Melanoma, and Psoriasis			
9.12.3 Drug Classes and Drugs			
HPV & Molluscum, Actinic Keratoses, BCC and SCC	Melanoma	Psoriasis	
		Topical	Systemic
5-fluorouracil imiquimod podofilox vismodegib	dabrafenib ipilimumab trametinib vemurafenib	calcipotriene glucocorticoids tazarotene	acitretin adalimumab cyclosporine etanercept infliximab methotrexate

Therapeutic uses

Outline the use of these drugs in the treatment of alopecia areata and androgenic alopecia.

9.12.3.1 Therapeutic uses

Outline the use of these drugs for the treatment of HPV & molluscum, actinic keratoses, BCC and SCC, and psoriasis.

Drugs Used for Treating Inflammatory Bowel Disease
9.12.4 Drug Classes and Drugs

Mesalamine-based therapy	Steroids	Immuno-suppressives	Biologicals	Drugs altering balance of enteric bacteria
balsalazide mesalamine olsalazine sulfasalazine	budesonide hydrocortisone prednisone	azathioprine mercaptopurine methotrexate	infliximab natalizumab	ciprofloxacin metronidazole *lactobacillus* spp. *saccharomyces boulardii*

9.12.4.1 Therapeutic uses
Drugs for treating ulcerative colitis and Crohn disease are also covered in the Gastrointestinal Section (8).

Drugs used for Nausea and Vomiting
9.12.5 Drug Classes and Drugs

5-HT Antagonists	Substance P/NK_1 Antagonist	Corticosteroids	Others
granisetron ondansetron	aprepitant	dexamethasone	metoclopramide nabilone olanzapine prochlorperazine scopolamine

9.12.5.1Therapeutic uses
Outline the use of these drugs in treating nausea and vomiting associated with chemotherapy, radiation, and postoperative.

Drugs used for treating Peptic Ulcer Disease and GERD
9.12.6 Drug Classes and Drugs

Inhibitors of Acid Secretion		Mucosal Protectants	Drugs for eradicating *H. pylori*	Antacids
H_2RAs	PPIs			
cimetidine famotidine nizatidine ranitidine	omeprazole	bismuth salts misoprostol sucralfate	amoxicillin bismuth clarithromycin metronidazole tetracycline inhibitors of acid secretion	$CaCO_3$ $Al(OH)_3$ $Mg(OH)_2$ $NaHCO_3$

9.12.6.1 Therapeutic uses
Differentiate between the use of these drugs in peptic ulcer disease and GERD.

Drug Treatment for Erectile Dysfunction		
9.12.7 Drug Classes and Drugs		
PDE5 Inhibitors	Prostaglandin Analog	Testosterone Replacement
sildenafil tadalafil vardenafil	alprostadil	methyltestosterone testosterone topical testosterone enanthate
9.12.7.1 Therapeutic uses Outline the use of these drugs in treating erectile dysfunction.		

Drugs for Allergic Reactions				
9.12.8 Drug Classes and Drugs				
Glucocorticoids	Decongestants	Anticholinergics	Anaphylaxis	Autacoid Antagonists
Fluticasone Prednisone	phenylephrine pseudoephedrine	ipratropium	epinephrine	antihistamines modulators of histamine release LT receptor antagonists
9.12.8.1 Therapeutic uses Outline the use of the drugs in each class in treating allergic disorders.				

Pharmacology of Tocolytics, Antenatal Drugs and Abortives				
9.12.9 Drug Classes and Drugs				
Tocolytics			Abortives	
Ca^{++} Blockers	β-Agonists	COX inhibitors		
nifedipine	terbutaline	indomethacin	methotrexate mifepristone misoprostol	betamethasone indomethacin magnesium sulfate
9.12.9.1 Therapeutic uses Outline the clinical uses of the drugs used in preventing preterm labor and in abortion. Outline the uses of betamethasone and indomethacin in antenatal and neonatal therapy, respectively.				
9.12.9.2 Clinical Pharmacology Evidence for efficacy of tocolytics in humans is less than Impressive. ACE inhibitors also contraindicated in pregnancy.				

10. CANCER PHARMACOLOGY

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10.1 Basic Principles of Cancer Chemotherapy
10.1.1 Content Recommendations
Explain the role of chemotherapy in the management of patients with cancer. Compare and contrast the strategies and outcomes from standard cytotoxic chemotherapy and targeted therapies. Describe the various limitations to effective drug treatment, including tumor burden at time of diagnosis, tumor genotype, patient comorbidities, drug access and cost. Define and explain the terms doubling time and growth fraction. Define the term cell cycle specificity, discuss its relevance to cancer treatment approaches, and classify the various anticancer drugs based on cell cycle specificity. Explain the concepts of tumor heterogeneity and tumor stem cells, and discuss how they impact cancer treatment. Explain the term *cell cycle specificity* and be able to classify the various anticancer drugs based on the cell cycle specificity. Describe the principles of combination chemotherapy in the treatment of cancer, including the use of surgery and/or radiation Define the terms induction, maintenance, adjuvant, and neoadjuvant chemotherapy. Explain the mechanisms of resistance to anticancer drugs. Describe adverse effects of anticancer drugs and approaches to minimizing adverse effects.

10.2 Anticancer Drugs

10.2.1 Drugs and Drug Classes

Adducting Agents	Antimetabolites
CYCLOPHOSPHAMIDE CISPLATIN CARBOPLATIN chlorambucil busulfan dacarbazine procarbazine ifosfamide melphalan Nitrosoureas (carmustine and lomustine) oxaliplatin temozolomide	CAPECITABINE CYTARABINE 5-FLUOROURACIL GEMCITABINE METHOTREXATE 6-mercaptopurine azacitidine fludarabine hydroxyurea pemetrexed pralatrexate thioguanine
Antibiotics	**Topoisomerase Inhibitors and Mitotic Spindle Poisons**
BLEOMYCIN DAUNORUBICIN DOXORUBICIN dactinomycin epirubicin idarubicin	<u>Topoisomerase Inhibitors</u> ETOPOSIDE IRINOTECAN teniposide topotecan <u>Spindle Poisons</u> VINCRISTINE PACLITAXEL docetaxel vinblastine vinorelbine

10.2.2 Content Recommendations

10.2.2.1 Physiology & Pathophysiology

Discuss the stages of the cell cycle and their function.

Illustrate the biochemical pathways of purine and pyrimidine biosynthesis.

Describe common sites of DNA damage and well-known DNA replication and repair pathways, including the specific roles of topoisomerases and mitotic spindles.

10.2.2.2 Mechanism of action

Describe the mechanism of action of various individual anticancer drugs under each class.

Describe the intracellular activation pathways of different antimetabolites.

Explain the use of leucovorin in high dose methotrexate therapy and as a sensitizing agent with 5-fluorouracil.

10.2.2.3 Pharmacokinetics

Explain the different bioactivation pathways required for the action of cyclophosphamide and capecitabine.

Describe acrolein as a toxic metabolite of some adducting agents, and discuss the role of IV hydration and treatment with sodium 2-mercaptoethane sulfonate (mesna) to neutralize acrolein.

Discuss the role of dexrazoxane in treating anthracycline extravasation and preventing doxorubicin-mediated cardiomyopathies.

10.2.2.4 Adverse effects

Describe the common toxicities for each class of anticancer drugs.

Describe the specific major toxicity of individual anticancer drugs.

Describe the cumulative dose-dependent toxicity of anthracyclines.

10.2.2.5 Therapeutic uses

Discuss the impact of both patient and tumor genotypes on drug choices and efficacy in cancer chemotherapy.

Evaluate whether a drug has broad therapeutic activity across a range of cancer types, or if a drug is only used in a small number of cancers.

10.2.2.6 Clinical Pharmacology

Evaluate a patient for possible drug interactions or comorbidities since these treatments have low therapeutic indices and are cytotoxic.

Describe the clinical pathophysiology of tumor lysis syndrome, and list the treatments for prophylaxis and treatment of this illness.

10.3 Pathway-Targeted Antineoplastic Agents

10.3.1 Drugs and Drug Classes

Kinase Inhibitors	Monoclonal Antibodies & Fusion Proteins	Miscellaneous Agents
ERLOTINIB IMATINIB LAPATINIB PALBOCICLIB abemaciclib afatinib crizotinib dasatinib gefitinib sorafenib sunitnib vemurafenib	CETUXIMAB NIVOLUMAB PEMBROLIZUMAB TRASTUZUMAB RITUXIMAB atezolizumab bevacizumab ipilimumab panitumumab pertuzumab	BORTEZOMIB EVEROLIMUS carfilzomib temsirolimus tretinoin vorinostat
		Antibody-Drug Conjugates
		IBRITUMOMAB TIUXETAN A DO-TRASTUZUMAB EMTANSINE
	Cellular & Gene Therapies	
	TISAGENLECLEUCEL axicabtagene ciloleucel brexucabtagene autoleucel sipuleucel-T	

10.3.2 Content Recommendations

10.3.2.1 Physiology and Pathophysiology

Discuss molecular pathways known to drive malignant progression of neoplastic disease.

Summarize the process of T-cell activation and explain its relevance to antineoplastic therapy with immune checkpoint inhibitors.

10.3.2.2 Mechanism of action

Compare and contrast pharmacologic strategies for targeted inhibition of oncogenic drivers.

Identify the molecular target and describe the mechanism of action of individual anticancer drugs under each class.

Distinguish primary and acquired drug resistance and common mechanisms of each.

10.3.2.3 Pharmacokinetics

Explain the pharmacokinetic limitations of monoclonal antibodies, fusion proteins, antibody-drug conjugates, and cell-based therapies.

10.3.2.4 Adverse effects

Identify the common toxicities of pathway-targeted antineoplastic agents and discuss why they are different from the common toxicities of cytotoxic antineoplastic agents.

List the rare, but serious, toxicities for individual pathway-targeted antineoplastic agents.

10.3.2.5 Therapeutic uses

List the major therapeutic indications of various pathway-targeted antineoplastic agents .

Explain the rationale for the use of drug combination therapy (e.g., antibody-drug conjugates) in cancer treatment.

Discuss the impact of both patient and tumor genotypes on drug choices and efficacy in cancer chemotherapy.

10.3.2.6 Clinical Pharmacology

Give examples of molecular biomarkers that can be used to predict therapeutic benefit and toxicity of pathway-targeted antineoplastic agents.

10.4 Drugs for Hormone Sensitive Cancers	
10.4.1 Drugs and Drug Classes	
Glucocorticoids	Antiestrogens
PREDNISONE dexamethasone methylprednisolone prednisolone	TAMOXIFEN fulvestrant raloxifene toremifene
Aromatase Inhibitors	Antiandrogens
EXEMESTANE ANASTRAZOLE aminoglutethimide letrozole	ABIRATERONE ACETATE BICALUTAMIDE apalutamide enzalutamide <u>GnRH Agonists</u> LEUPROLIDE goserelin

10.4.2 Content Recommendations

10.4.2.1 Physiology & Pathophysiology

Explain the role of hormone signaling in cancer cell growth.

10.4.2.2 Mechanism of action

Describe the mechanisms of action of the glucocorticoids in immune suppression and anticancer activities.

Explain how a GnRH agonist leads to suppression of androgenic signaling

Diagram how an aromatase inhibitor decreases estrogen signaling.

Compare and contrast the mechanisms of SERMs and SERDs.

10.4.2.3 Pharmacokinetics

Explain the two phases of GnRH agonist therapies for prostate cancer.

Explain why SERM pharmacokinetics is impacted in hepatically-impaired patients, but not renally-impaired patients.

10.4.2.4 Adverse effects

Describe dose-limiting toxicities of long-term corticosteroid use.

Explain how the use of anti-estrogens and aromatase inhibitors represent a double-edged sword in terms of benefits versus costs.

10.4.2.5 Therapeutic uses

Detail how the pathologic work-up of breast cancer determines the recommended course of treatment.

Describe how the consequences of prostate cancer therapy may present a barrier to patient compliance.

10.4.2.6 Clinical Pharmacology

Describe the clinical biomarkers that determine treatment approaches to hormone sensitive breast cancer.

10.5 Appendix
*** Additional anticancer drugs that are not as important during preclerkship undergraduate medical education**

10.5.1 Anticancer Drugs

Adducting agents

mechlorethamine

Antimetabolites

cladribine

Antibiotics

mitoxantrone
valrubicin

Cellular & Gene Therapies

idecabtagene vicleucel
lisocabtagene maraleucel

Kinase Inhibitors

alectinib
axitinib
bosutinib
cabozantinib
ceritinib
cobimetinib
dabrafenib
ibrutinib
idelalisib
lenvatinib
midostaurin
neratinib
niolotinib
osimertinib
pazopanib
ponatinib
regorafenib
ribociclib
ruxolitinib
trametinib
tucatinib
vandetanib

Monoclonal Antibodies & Fusion Proteins

alemtuzumab
avelumab
blinatumomab
daratumumab
dinutuximab
durvalumab
elotuzumab
necitumumab
obinutuzumab
ofatumumab
ramucirumab
ziv-aflibercept

Antiestrogens

megestrol acetate

Miscellaneous Agents

ixazomib
olaparib
venetoclax

Antibody-Drug Conjugates

brentuximab vedotin
fam-trastuzumab deruxtecan
inotuzumab ozogamicin
moxetumomab pasudotox
polatuzumab vedotin

Antiandrogens

flutamide
nilutamide

<u>GnRH Agonists</u>
buserelin
triptorelin

Glucocorticoids

betamethasone

Aromatase Inhibitors

fadrozole
formestane

11. ENDOCRINE PHARMACOLOGY

Subcommittee

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11.1 Introduction
Recommended Curriculum Equivalent: 0.5 hr
11.1.1 Content Recommendations
11.1.1.1 Physiology and pathophysiology Describe general functions of hormones and their target organs; principal types of hormones, and their structure-activity relationships, location, and types of receptors; and regulation of hormone synthesis and release (including feedback) involved in maintaining necessary hormone levels. Describe the etiology of endocrine diseases, including hormone deficiency/excess, receptor dysfunction, and hormone resistance.
11.1.1.2 Mechanism of action Describe the mechanisms of hormone action, including receptors and signal transduction pathways (receptor location, molecular events activated by hormones at cell membrane or intracellular receptors, and second messenger systems). Identify drugs used in the treatment of endocrine disorders, describing for each, its mechanism of action.
11.1.1.3 Actions on organ systems Describe the effects of stimulating hormone receptors on the organ systems.
11.1.1.4 Pharmacokinetics Describe the regulation of hormone synthesis, release, metabolism, and excretion; role of daily rhythms, patterns of release, binding proteins, modulating factors (e.g., neurotransmitters, release and release-inhibiting hormones) and measurement.

11.1.1.5 Therapeutic uses

Describe the therapeutic uses of hormones and hormone analogs, as agonists/antagonists.

Notes: Hormones include those released by the hypothalamus, anterior pituitary, posterior pituitary, Adrenal Cortex, Thyroid, Parathyroid, Endocrine Pancreas, Gonadal Hormones, and drugs used in treatment of Female and Male Urogenital System, and obesity.

Resources:

(1) USMLE Step 1 Content

(2) COMLEX Blueprint

(3) B.G. Katzung and T.W. Vanderah, Basic and Clinical Pharmacology, 15th edition (2021)

11.2 Hypothalamus and Anterior Pituitary

Recommended Curriculum Equivalent: 2.0 hr

11.2.1 Drug Classes and Drugs

Growth Hormone	Prolactin	Gonadotropins	ACTH	TSH
SOMATROPIN MECASERMIN SERMORELIN (GHRH) OCTREOTIDE Lanreotide PEGVISOMANT Lonapegsoma-tropin Bromocriptine	PROLACTIN BROMOCRIPTINE CABERGOLINE	GONADOTROPIN MENOTROPINS FOLLITROPIN alfa Urofollitropin CHORIONIC GONADOTROPIN -ALFA LEUPROLIDE Goserelin Buserelin Histrelin Nafarelin Triptorelin GANIRELIX Abarelix Degarelix	Cosyntropin	Thyrotropin

11.2.2 Content Recommendations

11.2.2.1 Physiology and pathophysiology

Describe release (GHRH, GnRH) and release-inhibiting (somatostatin, dopamine) hormones and trophic hormones (GH, prolactin, ACTH, TSH, LH and FSH) of the anterior pituitary.

Describe the regulation of growth hormone (GH) synthesis and secretion, including the roles of growth hormone releasing hormone (GHRH), glucose levels, somatostatin and dopamine.

Describe the physiologic role of GH, feedback regulation and the role of insulin-like growth factor 1 (IGF-1) in the secondary effects of GH. Describe the effects of deficiency of and excessive GH.

Describe the physiologic role of prolactin, feedback regulation and the effects of deficiency and excess.

Describe the physiologic role of GnRH, LH and FSH, ACTH, and TSH, feedback regulation, and effects of deficiency and excess.

11.2.2.2 Mechanism of action

Identify drugs acting as agonists and antagonists of hypothalamic-pituitary hormones, describing for each the mechanism of action.

11.2.2.3 Actions on organ systems

Describe the biological effects of GH analogs and drugs affecting growth hormone secretion and action on peripheral tissues.

Describe the biological effects of drugs altering secretion of prolactin on breast development and lactation; and the interrelationship with other hormones (e.g., growth hormone, estrogen, progesterone, glucocorticoids, oxytocin) involved in breast development and lactation

Describe the biological effects of analogs of GnRH, FSH and LH on secretion of gonadal hormones.

11.2.2.4 Pharmacokinetics

For each class of drugs, describe the pharmacokinetic factors (absorption, distribution, metabolism and excretion) affecting the route and time course of action.

11.2.2.5 Adverse effects, drug interactions and contraindications

Describe the adverse effects of GH therapy in children and adults.

Describe the adverse effects of drugs altering secretion of prolactin.

Describe the adverse effects of GNRH agonists and antagonists, used in treatment of infertility, prostate carcinoma, endometriosis and precocious puberty.

11.2.2.6 Therapeutic uses

Describe the therapeutic uses of GHRH, somatostatin analogs and pegvisomant.

Describe the therapeutic uses of drugs which alter the secretion of prolactin.

Describe the therapeutic uses of GnRH agonists and antagonists; and FSH and LH analogs.

Describe the importance of route of administration and therapeutic uses of GnRH analogs: intermittent (infertility) versus continuous administration (endometriosis, uterine fibroids, prostate cancer).

Describe the utility of ACTH stimulation test in diagnosing pituitary-adrenal disorders.

Notes/References

USMLE Step 1 Content

1) Endocrine system-Normal Processes: hypothalamus, posterior and anterior pituitary gland
2) Endocrine system-Abnormal Processes- hypothalamic endocrine disorders; pituitary disorders (including acromegaly/gigantism, galactorrhea, growth hormone deficiency, short stature, prolactinoma and hyperprolactinemia
3) Reproductive System- hypothalamic-pituitary- gonadal axis
4) Reproductive System-Abnormal processes

COMLEX Master Blueprint

Katzung and Vanderah, Basic and Clinical Pharmacology, 15th edition (2021)

11.3 Hypothalamus and Posterior Pituitary

Recommended Curriculum Equivalent: 1.0 hr

11.3.1 Drug Classes and Drugs

Vasopressin	Oxytocin
DESMOPRESSIN VASOPRESSIN CONIVAPTAN TOLVAPTAN	OXYTOCIN TOCOLYTICS (terbutaline, nifedipine)

11.3.2 Content Recommendations

11.3.2.1 Physiology and pathophysiology

Describe the effects of vasopressin on receptor subtypes and signal transduction systems in vascular smooth muscle and the kidney.

Describe the mechanisms by which vasopressin increases renal water reabsorption.

Describe the pharmacokinetics and actions of oxytocin on uterine smooth muscle and lactation.

11.3.2.2 Mechanism of action

Identify drugs that alter vasopressin release and actions and their mechanism of action.

Identify the mechanism of action of oxytocin and tocolytic drugs.

11.3.2.3 Actions on organ systems

Describe actions of vasopressin and analogs on the vasculature and renal water reabsorption.

Describe the actions of oxytocin and tocolytic drugs.

11.3.2.4 Adverse effects, drug interactions and contraindications

Describe the adverse reactions of vasopressin, desmopressin and the “vaptans”.

Describe the adverse reactions and contraindications for use of oxytocin and tocolytic drugs.

11.3.2.5 Therapeutic uses

Identify drugs used in the treatment of diabetes insipidus (nephrogenic and neurogenic) and Syndrome of Inappropriate Secretion of Antidiuretic Hormone (SIADH).

Identify the therapeutic uses of oxytocin and tocolytic drugs.

Notes/References

USMLE Step 1 Content:

(1) Hormones acting on the kidney

(2) Pituitary Disorders: Diabetes insipidus, SIADH

COMPLEX Master Blueprint

Katzung and Vanderah, Basic and Clinical Pharmacology, 15th edition (2021)

11.4 DRUGS AFFECTING THE ADRENAL CORTEX AND ENDOCRINE PHARMACOLOGY

11.4.1 Drug Classes and Drugs

Glucocorticoid-receptor agonists:	Glucocorticoid-receptor antagonists:	Mineralocorticoid-agonists:	Mineralocorticoid-antagonists:	Synthesis inhibitors:
HYDROCORTISONE (CORTISOL) DEXAMETHASONE PREDNISONE PREDNISOLONE Beclomethasone Betamethasone Budesonide Fluticasone Mometasone Triamcinolone	Mifepristone	ALDOSTERONE FLUDROCORTISONE	SPIRONOLACTONE Eplerenone	Aminoglutethimide Etomidate KETOCONAZOLE METYRAPONE Spironolactone Mitotane

11.4.2 Content Recommendations

11.4.2.1 Physiology and pathophysiology

- Describe the major steps and hormones involved in the hypothalamus-pituitary-adrenal (HPA) axis.
- Describe the regulation of adrenal corticosteroid and aldosterone synthesis by ACTH and angiotensin.
- Differentiate corticosteroid or aldosterone changes in adrenal disorders, e.g., Addison's Disease versus Cushing's Syndrome.

11.4.2.2 Mechanism of action

- Explain the molecular mechanisms of action of glucocorticoid and mineralocorticoid receptor agonists and antagonists.
- Explain how drugs that impact via 11-beta-steroid hydroxylase or other critical enzymes in steroid synthesis can lower levels of cortisol and impact other steroid hormone levels

11.4.2.3 Actions on organ systems

- Describe the actions of corticosteroids on intermediary metabolism, growth and development, electrolyte homeostasis, immune, and inflammatory responses.
- Describe the cellular/molecular mechanisms of action of corticosteroids on bodily functions (e.g., cardiovascular, endocrine, musculoskeletal, immune, pulmonary, central nervous system, gastrointestinal, ophthalmic, and other).
- Demonstrate knowledge of the important aspects of synthetic glucocorticoids that enhance pharmacodynamic activity (e.g., potency).
- Describe how the activity and application of glucocorticoids can vary based on the route of administration.

11.4.2.4 Pharmacokinetics

- Describe the significance of corticosteroid disposition (protein binding, biotransformation, enzyme induction) that may necessitate changes in dosage regimens.
- Describe the potential effects of long-term treatment with corticosteroids.

11.4.2.5 Adverse effects, drug interactions and contraindications

- List the adverse effects/contraindications related to corticosteroid use.
- List the adverse effects of excessive mineralocorticoid activity.
- Categorize important interactions between corticosteroids and other drugs that would require close monitoring and potential dose adjustments.

11.4.2.6 Therapeutic uses

- Explain the rationale for corticosteroid use in replacement therapy, as anti-inflammatory and immunosuppressive agents, and as diagnostic agents in hypothalamus-pituitary adrenocortical disease/dysfunction.
- Explain the use of fludrocortisone in replacement therapy.
- Explain the rationale for alternate day therapy and the necessity for slow withdrawal following chronic therapy with glucocorticoids.
- Explain the rationale for spironolactone in treating primary hyperaldosteronism.
- Explain how synthesis inhibitors are used to treat diseases associated with excessive steroid production.

11.4.2.7 Clinical Pharmacology

- Describe the effects of severe liver disease on the activation of prednisone to prednisolone in patients.

Describe the inhibitory effects of ketoconazole on cytochrome P450 and P-glycoprotein, and potential drug-drug interactions

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Notes

- Hodgens A, Sharman T. Corticosteroids. [Updated 2022 May 8]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK554612/
- Katzung B.G., & Vanderah T.W.(Eds.), (2021). *Basic & Clinical Pharmacology*, *15e*. McGraw Hill. https://accesspharmacy.mhmedical.com/content.aspx?bookid=2988&sectionid=250593594
- United States Medical Licensing Examination (USMLE) Content Outline (2022). https://www.usmle.org/sites/default/files/2022-01/USMLE_Content_Outline_0.pdf.

Relevance

Relevant USMLE topics

1) Endocrine System > Normal Processes > **Organ structure and function** > adrenal cortex, adrenal medulla
2) Endocrine System > Normal Processes > **Cell/tissue/structure and function, including hormone synthesis, secretion, action, metabolism** > peptide hormones; steroid hormones; renin-angiotensin system
3) Endocrine System > Abnormal Processes: Health and Health Maintenance, Screening, Diagnosis, Management, Risks, Prognosis > **Adrenal disorders:** corticoadrenal insufficiency (Addison disease); adrenal insufficiency, secondary; hypocortisolism; Cushing syndrome; hyperaldosteronism; neoplasms, benign and malignant (adrenal neuroblastoma, pheochromocytoma, adrenal carcinoma, adrenal adenoma, aldosteronoma, adrenal incidentaloma); delayed and precocious puberty; hypertensive endocrine disease
4) Endocrine System > Abnormal Processes: Health and Health Maintenance, Screening, Diagnosis, Management, Risks, Prognosis > **Hypothalamic endocrine disorders**
5) Endocrine System > Abnormal Processes: Health and Health Maintenance, Screening, Diagnosis, Management, Risks, Prognosis > **Adverse effects of drugs on the endocrine system:** drug, medicinal, and biologic substance effects; exogenous steroid suppression of adrenal glands, anabolic steroids

11.5 DRUGS AFFECTING THYROID HORMONE FUNCTIONS AND ENDOCRINE PHARMACOLOGY

11.5.1 Drug Classes and Drugs

Thyroid products/Synthetic thyroid hormones:	LEVOTHYROXINE (T4) LIOTHYRONINE (triiodothyronine, T3) Liotrix	Carbimazole	Iodide salts	Ipodic acid (ipodate)
Antithyroid agents:	METHIMAZOLE (MMI) PROPYLTHIOURACIL (PTU) POTASSIUM IODIDE	RADIOIODINE 131 (^{131}I)	PROPRANOLOL Nadolol	Teprotumumab

11.5.2 Content Recommendations

11.5.2.1 Physiology and pathophysiology

- Outline the main steps of the hypothalamus-pituitary-thyroid gland axis for thyroid hormone synthesis.
- Outline the key regulatory steps for thyroid hormone deiodination and peripheral conversion.
- Explain the mechanisms by which thyroid hormones regulate cellular function.
- Describe the diagnostic signs/symptoms of hypothyroidism and its severe complication, myxedema.
- Explain how hypothyroidism can alter drug therapy for other concurrent diseases.
- Describe the diagnostic signs/symptoms of hyperthyroidism and its severe complication, thyroid storm.
- Explain how hyperthyroidism can alter drug therapy for other concurrent diseases.

11.5.2.2 Mechanism of action

- Explain the molecular mechanisms of action for antithyroid agents.
- Explain the molecular mechanisms of action for thyromimetic agents.
- Explain the molecular mechanism of action for the thyroid eye disease treatment, teprotumumab.

11.5.2.3 Actions on organ systems

- Delineate the relationship between thyroid hormones and the actions of catecholamines.
- Describe the rational for the use of certain beta-blockers (propranolol or nadolol) in the treatment of hyperthyroidism.

11.5.2.4 Pharmacokinetics

- Describe the pharmacokinetic rationale for selecting the most appropriate form of thyroid hormone as replacement therapy.
- Identify the best index of adequate replacement therapy with thyroid hormone.
- Differentiate the kinetic parameters, production, half-life, and potency for T4 and T3 thyroid hormones.
- Describe the pharmacokinetic rationale for selecting the most appropriate anti-thyroid drug for treating hyperthyroidism (diffuse toxic goiter) in a non-pregnant versus a pregnant female.

11.5.2.5 Adverse effects, drug interactions and contraindications

- Describe the adverse effects of anti-thyroid medications and identify those that are potentially life-threatening.
- Understand why methimazole is contraindicated during the first trimester of pregnancy.
- Describe the adverse reactions of thyromimetic agents

11.5.2.6 Therapeutic uses

- Describe the therapeutic use of thyromimetic agents in the treatment of hypothyroid disease.
- Describe the caution necessary when replacing thyroid hormone in a patient with a history of coronary artery disease.
- Describe the rationale and order of administration of drugs given to treat thyroid storm.
- Provide the rationale for the uses of drugs/radioiodine in treating hyperthyroidism and explain their mechanism(s) of action.
- Describe the consequences of radioiodine use.

11.5.2.7 Clinical Pharmacology

- Thyroxine is indicated for the treatment of hypothyroidism. The use of triiodothyronine is dangerous because of its increased potency and rapid and potential adverse effects on cardiac function.
- Propylthiouracil is the antithyroid drug of choice in the first trimester of pregnancy because of its shorter half-life and its lesser tendency to cross the placenta. Methimazole should not be used during the first trimester of pregnancy because it crosses the placenta and can cause fetal abnormalities. When changing from one drug to another, a 1:20 potency ratio for methimazole to propylthiouracil is recommended.

Although propranolol and nadolol actively decrease the conversion of T4 to T3, these beta-blockers are not used to manage hyperthyroidism to reduce T3 production. Beta-blockers are indicated in thyroid storm to decrease the enhancement of catecholamine stimulation of cardiac contractility in the hyperthyroid state.

Notes

- Armstrong M, Asuka E, Fingeret A. Physiology, Thyroid Function. [Updated 2022 Mar 18]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK537039/
- Katzung B.G., & Vanderah T.W.(Eds.), (2021). *Basic & Clinical Pharmacology, 15e*. McGraw Hill. https://accesspharmacy.mhmedical.com/content.aspx?bookid=2988&sectionid=250593594
- United States Medical Licensing Examination (USMLE) Content Outline (2022). https://www.usmle.org/sites/default/files/2022-01/USMLE_Content_Outline_0.pdf

Relevance

Relevant USMLE topics

1) Endocrine System > Normal Processes > **Organ structure and function** > thyroid gland
2) Endocrine System > Normal Processes > **Cell/tissue/structure and function, including hormone synthesis, secretion, action, metabolism** > peptide hormones; thyroid hormones
3) Endocrine System > Abnormal Processes: Health and Health Maintenance, Screening, Diagnosis, Management, Risks, Prognosis > **Thyroid disorders:** cyst, nodule; euthyroid sick syndrome; goiter (euthyroid-normal thyroid function with goiter); hypothyroidism; hyperthyroidism, including thyrotoxicosis and thyroid storm; thyroiditis, including Hashimoto; Graves disease; neoplasms (benign cysts and nodules, thyroid cancer including papillary, follicular, medullary, and anaplastic); thyroid deficiency from pituitary disorder; infertility due to thyroid disease; secondary hypothyroidism and hyperthyroidism
4) Endocrine System > Abnormal Processes: Health and Health Maintenance, Screening, Diagnosis, Management, Risks, Prognosis > **Hypothalamic endocrine disorders**
5) Endocrine System > Abnormal Processes: Health and Health Maintenance, Screening, Diagnosis, Management, Risks, Prognosis > **Congenital disorders:** congenital hypothyroidism
6) Endocrine System > Abnormal Processes: Health and Health Maintenance, Screening, Diagnosis, Management, Risks, Prognosis > **Adverse effects of drugs on the endocrine system**
7) Pregnancy, Childbirth, & the Puerperium > Abnormal Processes > **Systemic disorders affecting pregnancy, labor and delivery, and puerperium:** thyroid disorders, hypothyroidism, hyperthyroidism

11.6 PARATHYROID (calcium and phosphate homeostasis)

Recommended Curriculum Equivalent: 0.5 hr

11.6.1 Drug Classes and Drugs

Bisphosphonates (Alendronate, Ibandronate, Risedronate, Zoledronate)
Calcitonin
Calcitriol
Calcium gluconate
Cinacalcet
Denosumab
Furosemide
Parathyroid hormone (Teriparatide; aboloparatide)
Prednisone
Sevelamer
Sodium fluoride
Vitamin D (calcitriol/cholecalciferol/ergocalciferol)

11.6.2 Content Recommendations

11.6.2.1 Physiology and pathophysiology

Describe the regulation of calcium and phosphate homeostasis and the physiological actions of parathyroid hormone (PTH), calcitonin (CT) and 1,25dihydroxyvitamin D_3 [1,25-$(OH)_2D_3$];
Describe the mechanisms regulating biosynthesis and secretion of PTH and CT.
Differentiate the effects of PTH, CT and calcitriol on GI tract, kidneys and bones in terms of their effects on blood calcium and phosphate levels.
Describe the role(s) of kidney, liver and GI tract in vitamin D homeostasis.
Describe the role of PTH, calcitriol, osteoprotegerin, RANK-ligand, and estrogen in bone remodeling.

11.6.2.2 Mechanism of action

Explain the molecular mechanism of action of above drugs used in the management of disorders affecting calcium and phosphate metabolism.

11.6.2.3 Adverse effects, drug interactions and contraindications

Describe the mechanism of the potential adverse effects of bisphosphonates, calcitonin, cinacalcet, 1,25-$(OH)_2D_3$ and calcium supplements, and teriparatide.
Describe clinically significant drug interactions and contraindications of above drugs.

11.6.2.4 Therapeutic uses

Compare and contrast the treatment of hypo- and hyperparathyroidism.
Describe the role of cholecalciferol and calcium supplements in the prevention and management of rickets/osteomalacia, and vitamin D deficiency.
Describe the therapeutic role of cinacalcet, sevelamer, and calcitriol in chronic renal failure.
Describe the role of bisphosphonates and loop diuretics in managing hypercalcemia of malignancy.
Describe the clinical value of bisphosphonates and CT in the treatment of: hypercalcemia, Paget's disease, osteoporosis (postmenopausal and glucocorticoid-induced).

11.7 THE ENDOCRINE PANCREAS

Recommended Curriculum Equivalent: 1.5 Hr

11.7.1 Drug Classes and Drugs

ACARBOSE (alpha-glucosidase inhibitors)
Diazoxide
EXENATIDE (Incretin mimetics)
Glucagon
GLIPIZIDE (Sulfonylurea)Chlorpropamide
Glyburide
INSULINS (aspart, degludec, glulisine, lispro, regular, NPH, detemir, glargine)
METFORMIN (Biguanides)
PIOGLITAZONE (Thiazolidinediones)
Pramlintide (amylin analogs)
REPAGLINIDE (meglitinides)
CANAGLIFLOZIN (Sodium-Glucose Co-Transporter 2 (SGLT2) Inhibitors)
dapagliflozin,
empagliflozin
SITAGLIPTIN (Dipeptidyl Peptidase-4 Inhibitors)
Saxagliptin
Linagliptin
Tirzepatide

11.7.2 Content Recommendations

11.7.2.1 Physiology and pathophysiology

Describe the normal daily patterns insulin secretion and changes that occur in different types of diabetes mellitus.
Describe the effects of insulin and glucagon on intermediary metabolism and ion transport.
Describe the effects of incretin hormones, esp. GLP-1 on insulin and glucagon secretion.
Describe the effects of amylin protein on glucagon secretion.
Describe the pathophysiology of the primary types of diabetes mellitus (bihormonal disease – insulin and glucagon), and their sequelae: diabetic ketoacidosis and nonketotic hyperosmolar coma.

11.7.2.2 Mechanism of action

Explain the molecular mechanism of action of each drug in each drug class.

Explain the mechanisms by which oral anti-diabetic agents may impact other physiological process relevant to co-morbidities associated with diabetes (eg.. obesity, heart function, kidney function)

11.7.2.3 Pharmacokinetics

Describe the pharmacokinetic (onset and duration of action) rationale for the use of insulin preparations in 'split-mixed' or continuous s.c. infusion.
List commonly used drugs with which sulfonylurea compounds are known to interact and the postulated mechanisms for these interactions (first vs. second generation).
Identify the route of administration for medications used to treat diabetes

11.7.2.4 Adverse effects, drug interactions and contraindications

Describe the clinical manifestations and management of overdose with insulin and oral hypoglycemic agents, respectively.

11.7.2.5 Therapeutic uses

Identify therapeutic indications for drugs in treating type I, type II, or gestational diabetes

Describe underlying co-morbidities that impact the choice of agent

Discuss how pharmacokinetic properties, such as onset, duration, and route of administration, of diabetic agents influence how and why certain medications are selected for specific indications

Describe the relative roles of insulin and oral hypoglycemics in the treatment of type I and type II diabetes mellitus.

Discuss the use of recombinant DNA insulin preparations and the insulin pumps that are employed in certain patients.

Identify major drug interactions that can impact medication efficacy and glycemic control for patients with diabetes

<table>
<tr><th colspan="3">11.8 GONADAL HORMONES</th></tr>
<tr><td colspan="3">Recommended Curriculum Equivalent – Variable (See note below)</td></tr>
<tr><th colspan="3">11.8.1 Drug Classes and Drugs</th></tr>
<tr><td colspan="2">Estrogen, progestin, and progesterone agonists</td><td>Androgen agonists</td></tr>
<tr><td>Estrogen agonists

ETHINYL ESTRADIOL
conjugated/esterified estrogens
estradiol 17ß
estrone
diethylstilbestrol (DES)
Phytoestrogens</td><td>Progestins or progesterone agonists

LEVONOGESTREL*
MEDROXYPROGESTERONE
NORETHINDRONE*
norgestimate
norgestrel*
PROGESTERONE
Desogestrel
drospirinone
etonogestrel</td><td>danazol
dehydroepiandrosterone
Fluoxymesterone
methyltestosterone
OXANDROLONE
TESTOSTERONE
DIHYDROTESTERONE (DHT)

*Note: some progestins also act as androgen agonists</td></tr>
<tr><td colspan="2">Selective Estrogen Receptor Modulators (SERMS) and Selective Estrogen Receptor Down-regulators (SERD)</td><td>Androgen antagonists</td></tr>
<tr><td colspan="2">RALOXIFENE
TAMOXIFEN
Toremifene
Bazedoxifene
CLOMIPHENE
FULVESTRANT</td><td>FLUTAMIDE
Bicalutamide
FINASTERIDE
drospirinone</td></tr>
<tr><td colspan="2">Aromatase Inhibitors (AIs)</td><td>Androgen Synthesis Inhibitors</td></tr>
<tr><td colspan="2">ANASTROZOLE
Letrazole
EXEMESTANE</td><td>SPIRONOLACTONE
Ketoconazole
FINASTERIDE</td></tr>
<tr><td colspan="2">Progesterone antagonists or modulators</td><td>Gonadotropin-related drugs</td></tr>
<tr><td colspan="2">MIFEPRISTONE
Ulipristal</td><td>LEUPROLIDE**
DEGARELIX**

**Note: These drugs are also covered in the HPA-Pharmacology Objectives but are often used to reduce gonadotropin levels (androgens and estrogens)</td></tr>
<tr><td colspan="3"></td></tr>
</table>

11.8.2 Content Recommendations
11.8.2.1 Physiology and pathophysiology Describe gonadal functions of the female and male reproductive system Explain their regulation by gonadotropins. Identify sources of estrogen, progesterone, and androgens Characterize the roles of gonadotropins in sexual differentiation, puberty, and sexual behavior. Define menopause and document pathophysiological implications of hypoestrogenic and/or hypo -androgenic states Explain concerns and risks associated with gonadal hormone hyperfunction (precocious puberty, hyperandrogenism, excessive or unopposed estrogen, and gonadotropin hormone-responsive neoplasms)
11.8.2.2 Mechanism of action Explain the therapeutic mechanism of action of each drug in each drug class. Differentiate between the mechanisms of selective estrogen receptor modulators (SERMs), estrogen receptor antagonists, and estrogen synthesis inhibitors.
11.8.2.3 Actions on organ systems Describe the effects of estrogen on: cardiovascular function, coagulation, metabolism, electrolyte and water balance, bone remodeling, cognition, mood and sleep regulation, reproductive function, cell growth, skin, plasma proteins, blood lipids, and hepatic function Describe the effects of estrogens on other physiological hormones as well as on laboratory tests, Describe the effects of androgens on growth and development. Delineate the importance of dihydrotestosterone effects on prostate and other organs. Compare anabolic actions vs. androgenic actions of androgens. Predict the physiological effects (therapeutic and adverse) of antagonizing estrogen or progesterone, receptors and/or depleting estrogen or progesterone in females. Predict the physiological effects (therapeutic and adverse) of antagonizing androgens receptors and/or depleting androgens in males.
11.8.2.4 Pharmacokinetics Describe differences in absorption, distribution, and elimination between synthetic and natural estrogens, including phytoestrogens. Compare the routes of administration, absorption, and relative duration of action of synthetic progestins, progesterone agonists and antagonists, and androgen agonist and antagonists, Compare the routes of administration, absorption and relative duration of SERMs, agents used to decease synthesis of estrogen or androgens.
11.8.2.5 Adverse effects, drug interactions and contraindications List major adverse effects and contraindications for estrogens and progestins alone and in combination Differentiate between the adverse effects of progestins based on relative potency to stimulate androgenic receptors. Explain adverse effects of SERMs, estrogen antagonists, and estrogen synthesis inhibitors. Explain adverse effects of androgen antagonists and androgen synthesis inhibitors. Describe the adverse effects of progesterone antagonists. List the most common drug interactions with gonadotropin therapeutics. Describe the adverse effects of androgens and anabolic steroids when used in male or females.

11.8.2.6 Therapeutic uses

Describe the use of drugs such as clomiphene and gonadotropic drugs for the treatment of infertility.

List types of estrogen-containing hormonal contraceptive agents.

Compare and contrast the androgenicity of various progestins used in contraception.

Compare the benefits and concerns associated with various dosage schedule (e.g., biphasics, triphasics) and routes of administration (oral, transdermal patch, vaginal ring, etc) for contraception using combination (estrogen-progestin) therapy.

List agents used for postcoital contraception.

Describe other gynecologic therapeutic and diagnostic uses of estrogens and progestin-based therapeutics

Describe the rationale for use of progestin-only contraception as well as long-acting progestins.

Describe the rationale and appropriate uses for the replacement of estrogens and estrogen/progestin in postmenopausal women.

Describe the use of SERMs, estrogen receptor antagonists, and aromatase inhibitors in treatment of breast cancer.

Characterize the use of SERMs in post-menopausal women to protect bone.

Identify appropriate use of progesterone antagonists as abortifacients.

Describe the uses of androgen antagonists, androgen synthesis inhibitors, and other types of hormonal therapy in the treatment of prostate hyperplasia and prostate cancer.

Notes:

1. Multiple sessions may be necessary in integrated curricula to cover effectively all these therapeutics in the context of greatly differing therapeutic indications (eg…contraception, breast cancer treatment, hormone replacement, prostate hyperplasia, infertility, many more).
2. Clinically estrogens are prescribed with a progestin or progesterone in women with a uterus so clinically relevant discussion must encompass the effects of these drugs together.

11.9 FEMALE UROGENITAL SYSTEM

Recommended Curriculum Equivalent – Variable (See note above)

11.9.1 Drug Classes and Drugs

Oxytocics & Uterine stimulants	Tocolytics – none FDA Approved but they are still used off label
Carboprost tromethamine Dinoprostone ERGONOVINE MIFEPRISTONE MISOPROSTOL OXYTOCIN	INDOMETHACIN magnesium sulfate Terbutaline 17-hydroxyprogesterone Nifedipine

11.9.2 Content Recommendations

11.9.2.1 Physiology/pathophysiology

Describe the receptors mediating uterine myometrial contraction and relaxation.

Explain the physiological effects of oxytocin.

Discuss the physiological effects of prostaglandins on the uterus and cervix.

Explain how the progression of gestation and labor alter the responsiveness of uterine myometrial tissue.

11.9.2.2 Mechanism of action

Explain the therapeutic mechanism of action of each drug in each drug class.

11.9.2.3 Actions on organ systems

Describe the effects of oxytocic agents on the cervix and uterus when administered to induce labor.

Explain the effects of oxytocin on water regulation.

Predict the physiological effects of administering tocolytic agents systemically on the blood sugar, cardiovascular function, and smooth muscle relation.

11.9.2.4 Pharmacokinetics

State the usual route(s) of administration, onset and duration of action of the various oxytocic agents.
State the usual route(s) of administration as well as onset and duration of action of the various tocolytic agents.

11.9.2.5 Adverse effects, drug interactions and contraindications

Describe the potential adverse effects of the oxytocic agents in the mother (uterine, extrauterine) and in the infant.

Explain the adverse effects of tocolytic agents on the mother and baby.

Identify major contraindications to use of oxytocic or tocolytic agents.

11.9.2.6 Therapeutic uses

Describe the clinical use of the individual oxytocics.

Discuss the utilization of mifepristone versus prostaglandins and oxytocics in therapeutic abortion.

Identify the potential benefits and risks of administering tocolytic agents to the mother and baby.

Notes

No tocolytics are FDA approved but they are used off label clinically.

11.10 MALE UROGENITAL SYSTEM

Recommended Curriculum Equivalent – Variable (See note above)

11.10.1 Drug Classes and Drugs

Alpha1 adrenergic antagonists	**Alpha Reductase Inhibitors**
Alfuzosin Silodosin TAMSULOSIN TERAZOSIN Doxazosin	FINASTERIDE Dutasteride
PDE Inhibitors	**Other erectile dysfunction drugs**
Alprostadil SILDENAFIL	Alprostadil (Prostaglandin E1)

11.10.2 Content Recommendations

11.10.2.1 Physiology and pathophysiology

Describe the neuroendocrine factors that regulate functions of the male urogenital tract.
Predict the effects of prostate smooth muscle contraction and relaxation on urination.
Explain the pathophysiological processes underlying benign prostate hyperplasia and prostate cancer.
Describe the physiological processes involved in erection and ejaculation during male sexual responses.
Identify drugs used for other purposes that may contribute to erectile dysfunction.

11.10.2.2 Mechanism of action

Explain the mechanism of action of each drug in each drug class.

Discuss how mechanism of action of the drugs is relevant to their clinical use.

11.10.2.3 Pharmacokinetics

Describe the route of administration, absorption, distribution, and elimination for drugs in each class.

Identify drugs where the route of administration may limit use.

11.10.2.4 Adverse effects, drug interactions and contraindications

List the major or most common adverse effects of drugs from each class.

Explain major contraindications of drugs from each class.

Identify drug interactions, especially those with significant risk of morbidity and mortality.

11.10.2.5 Therapeutic uses

Identify drugs that can be used to treat benign prostatic hyperplasia.
Explain the goals of different classes of drugs used to treat benign prostatic hyperplasia.
Describe drugs used to treat erectile dysfunction (ED) and identify appropriate uses in patients with different underlying comorbidities.

Notes

Androgen antagonists used to treat prostate cancer are listed in the gonadal hormone section.

Drug interactions like PDE inhibitors and vasodilators like nitroglycerin should be covered as this presents a significant risk for deleterious consequences (eg,severe hypotension)

11.11 OBESITY

Recommended Curriculum Equivalent: 1 hr

11.11.1 Drug Classes and Drugs

PHENTERMINE
PHENTERMINE + TOPIRAMATE
ORLISTAT
NALTREXONE + BUPROPION
LIRAGLUTIDE/SEMAGLUTIDE
Tirzepatide

11.11.2 Content Recommendations

11.11.2.1 Physiology and pathophysiology

Describe the neuroendocrine factors that regulate feeding and satiation.

11.11.2.2 Mechanism of action

Identify drugs used in the treatment of obesity; describing for each: molecular mechanism of action.

11.11.2.3 Adverse effects, drug interactions and contraindications

List the adverse effects, drug interactions and contraindications of each of the drugs.

11.11.2.4 Therapeutic uses

List the drugs used in addition to diet, exercise and behavioral modification in short-term and long-term treatment of obesity.

11.11.2.5 Clinical Pharmacology

Diet, exercise and behavioral modification are primary interventions in treatment of obesity. Drug therapy is added as needed.

Surgical management has been beneficial in treatment of obese patients.

Notes/Resources: Katzung and Vanderah: Basic and Clinical Pharmacology, 15th edition (2021); Medical Letter (2022)

Relevance

USMLE topic	**Resources**
1) Normal Processes – Adipose tissue 2) Abnormal processes – systemic disorders affecting the endocrine system 3) Abnormal processes – metabolic and regulatory processes	Katzung and Vanderah: Basic and Clinical Pharmacology, 15th edition (2021); Medical Letter (2022)

12. HEMOSTASIS AND BLOOD FORMING ORGANS

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12.1 Hemostasis and Blood Forming Organs	
Recommended Curriculum Equivalent: 1.5 hr	
12.1.1 Drugs for Treating Anemia	
Minerals	Vitamins
DEFEROXAMINE FERROUS SULFATE ferrous gluconate iron dextran	CYANOCOBALAMIN FOLIC ACID VITAMIN B_{12}
Hematopoietic growth factors	
ERYTHROPOIETINS EPOETIN ALFA Darbepoetin	Myeloid Growth Factors Pegfilgrastim Sargramostim Thrombopoietic Growth Factors Interleukin-11 Thrombopoietin
12.1.2 Content Recommendations	
12.1.2.1 Physiology and pathophysiology Diagram the normal physiological control of hematopoietic growth factors and the effect of kidney failure on erythropoiesis. Relate factors that can lead to abnormal iron balance including genetic hemochromatosis to the iron absorption and transport pathways. Describe the biochemical systems, which are impaired in B-12 and folic acid deficiency, and the role of cyanocobalamin and folic acid in correcting the metabolic defect in DNA thymine and methionine synthesis.	
12.1.2.2 Mechanism of action Explain the molecular mechanism of action of each drug in each drug class.	
12.1.2.3 Actions on organ systems Describe the pharmacological effects of each class of drugs on the hematopoietic system.	
12.1.2.4 Pharmacokinetics Describe the possible etiologies which should be considered if a delayed or diminished response to doses of recombinant erythropoietin within the recommended dose range occurs. Analyze how the pharmacokinetics and therapeutic effects of epoetin alpha and darbepoetin alpha differs between normal and anemic dialysis patients. Describe the sources, transport, metabolism, storage, and excretion of vitamin B-12 and folic acid. State the factors, which influence the bioavailability of vitamin B-12 and folic acid.	

12.1.2.5 Adverse effects, drug interactions and contraindications

Describe the principal adverse effects and contraindications of the drugs in each class.

Describe the clinically important drug interactions of the drugs in each class.

Identify adverse events associated with erythropoietin use in cancer patients, and black box warning on erythropoietin preparations.

12.1.2.6 Therapeutic uses

Apply the criteria for oral therapy versus parenteral iron therapy to a patient with iron deficiency anemia. Consider the associated adverse effects and the predicted rates of response to the two therapies.

Describe the risks of acute iron poisoning in children and its treatment.

Evaluate the pharmacologic management of chronic iron overload disease (e.g., secondary to chronic blood transfusion, iron absorption disturbances, etc.).

Explain the appropriate management of the patient with a megaloblastic anemia with respect to both acute and chronic management, vitamin dosage and expected response.

Compare the possible metabolic reasons why folic acid will correct the erythropoietic lesion but not the neurologic lesion in Addisonian pernicious anemia.

Explain the rationale for the use of folic acid in patients with elevated serum levels of homocysteine or spina bifida.

Compare the therapeutic applications for myeloid growth factors with those for thrombopoietic growth factors.

Differentiate approaches to treatment of folic-dependent vs B12-dependent megaloblastic anemia; describe how laboratory tests guide choice of treatment.

Describe cancer vs non-cancer indications for myeloid growth factors. Delineate specific types of cancer where these growth factors are contradicted.

12.1.2.7 Clinical Pharmacology

In chronic kidney disease, iron absorption from the gastrointestinal tract is often impaired. Intravenous iron may be considered and may decrease the dose of more expensive erythropoiesis-stimulating therapies. Caution in that i.v. high molecular weight iron preparations are associated with increased risk of anaphylaxis.

12.1.2.8 Relevance

USMLE topic Hematopoietic and Lymphoreticular Systems-Abnormal Processes-Anemia of Chronic Disease	**Principles of therapeutics** Treatment of anemia, drugs stimulating erythrocyte production
AAMC Medical School Objectives Project Report X Patient Safety – Table 1	**Topic C:** Drug treatment of common conditions, **Topic D:** Management of less common but severe medical conditions and emergencies.

12.2 Anticoagulant Drugs

Recommended Curriculum Equivalent: 1 hr

12.2.1 Drug Classes and Drugs

Indirect Thrombin Inhibitors	Direct Thrombin Inhibitors	Factor Xa Inhibitors	Inhibitors of Clotting Factor Synthesis
HEPARIN Low Molecular Weight Heparins (LMWH) PROTAMINE SULFATE (antidote)	DABIGATRAN bivalirudin argatroban Idarucizumab (antidote)	ENOXAPARIN RIVAROXABAN fondaparinux Andexanet-alfa (antidote)	WARFARIN VITAMIN K (antidote)

12.2.2 Content Recommendations

12.2.2.1 Physiology and Pathophysiology

Explain the role of the coagulation cascade in the regulation of hemostasis.

Describe the synthesis of the vitamin K-dependent clotting factors and explain the role of antithrombin in the regulation of hemostasis.

Examine the pathogenesis of venous thrombosis.

12.2.2.2 Mechanism of Action

Explain the molecular mechanism of action of the drugs in each drug class.

Compare the structural features of unfractionated heparin, low molecular weight heparins, direct thrombin inhibitors and factor Xa inhibitors that determine their target specificity.

Compare the effect of direct vs. indirect thrombin and factor Xa inhibitors on their free and clot-bound targets.

Relate the structural similarity of warfarin to vitamin K to explain the mechanism of action of inhibitors of clotting factor synthesis.

Explain the effect of warfarin on anticoagulant factors protein S and protein C.

12.2.2.3 Actions On Organ Systems

Analyze the effect of heparin on platelet aggregation and plasma lipids.

Explain how the anticoagulant responses to heparin and warfarin are monitored clinically using aPTT and INR, respectively.

12.2.2.4 Pharmacokinetics

Identify the anticoagulants that are orally effective vs. those that must be given parenterally.

Compare the rates of onset of action of heparin, LMWH, Direct thrombin inhibitors and Factor Xa inhibitors with warfarin in regard to their routes of administration and mechanisms of action.

Apply the effects of warfarin on vitamin K-dependent clotting factor turnover to its anticoagulant activity.

Explain how genetic polymorphisms in *CYP2C9* and *VKORC1* can affect the patient response to warfarin.

12.2.2.5 Adverse Effects, Drug Interactions and Contraindications

State the principal complication of anticoagulant therapy (bleeding) and describe the adverse effects and contraindications of the drugs in each class.

Describe the incidence and time to onset of heparin-induced thrombocytopenia.

Explain how protamine and vitamin K are used as antidotes to excessive bleeding caused by heparin and warfarin, respectively.

Describe the effects of warfarin therapy during pregnancy on the developing fetus.

Discuss the disease, drug, food and herbal interactions with warfarin; explain how dietary vitamin K can affect warfarin therapy.

12.2.2.6 Therapeutic Uses

Evaluate parenteral and oral anticoagulant therapy for initial and long-term management of patients with venous thrombosis and pulmonary embolism; formulate a plan for transition from heparin to warfarin outpatient therapy.

Formulate a plan for the pharmacological management of thromboembolic complications from heparin-induced thrombocytopenia.

Apply the goals of warfarin therapy to its use in patients with:

atrial fibrillation
prosthetic heart valves
myocardial infarction
stroke

Defend the advantages/disadvantages of treatment with dabigatran or rivaroxaban, instead of warfarin for oral anticoagulant therapy.

12.2.2.7 Clinical Pharmacology

Patients receiving heparin for more than 4 days have an up to 5% risk of developing heparin-induced thrombocytopenia. Non-heparin anticoagulant alternatives are used to treat this condition, including fondaparinux, a factor X inhibitor, that is used off label. Its advantages include once daily, subcutaneous administration and the lack of effect on INR. It is important to remember that fondaparinux has no antidote for its infrequent causation of a major bleeding episode. The drug may also accumulate in patients with renal insufficiency and is contraindicated in patients with a creatinine clearance of < 30 ml/min.

Dabigatran and rivaroxaban were designed as alternatives to warfarin, but both also predispose patients to high risk for stroke, serious bleeding and blood clots. Like fondaparinux, they accumulate in patients with renal insufficiency, and interact with many of the same drugs that interact with warfarin. As a P-glycoprotein substrate, dabigatran's use must be reconsidered during concurrent administration of drugs that induce or inhibit P-glycoprotein.

12.2.2.8 Relevance

USMLE topic	**Principles of therapeutics**
Hematopoietic and Lymphoreticular Systems-Abnormal Processes-Hemorrhagic and Hemostatic Disorders	anticoagulants
AAMC Medical School Objectives Project Report X Patient Safety – Table 1	**Topic C:** Drug treatment of common conditions, **Topic D:** Management of less common but severe medical conditions and emergencies.

12.3 Antiplatelet Drugs

Recommended Curriculum Equivalent: 0.75 hr

12.3.1 Drug Classes and Drugs

Cyclooxygenase Inhibitors	ADP $P2Y_{12}$ Inhibitors	Phospho-diesterase Inhibitors	GPIIb/IIIa inhibitors	Inhibitors of PAR-1
ASPIRIN (acetylsalicylic acid) ibuprofen	CLOPIDOGREL prasugrel ticagrelor	dipyridamole	TIROFIBAN eptifibatide	VORAPAXAR

12.3.2 Content Recommendations

12.3.2.1 Physiology and pathophysiology

Explain the role of platelet aggregation in the regulation of hemostasis.
Describe the pathogenesis of thrombosis with respect to the platelet activation.

12.3.2.2 Mechanism of action

Explain the molecular mechanism of action of each drug in each drug class.
Describe how inhibition of prostaglandin synthesis affects platelet aggregation, specifically the role of COX-1 and COX-2.
Compare differences and similarities in mechanism of action for antiplatelet drugs: e.g., aspirin, dipyridamole, clopidogrel, abciximab, vorapaxar.

12.3.2.3 Actions on organ systems

Identify the site of action of each drug in the platelet aggregation process.

12.3.2.4 Pharmacokinetics

Contrast the effects and time course of aspirin with nonsteroidal anti-inflammatory agents (NSAIDs) and cyclooxygenase 2 (COX2) inhibitors on platelet function.
Demonstrate how manipulation of the dosing regimen for aspirin can reduce adverse effects, particularly on the GI tract.
Describe difference in routes of administration for different classes of antiplatelet drugs.
Explain how genetic polymorphisms in *CYP2C19* can affect the patient response to clopidogrel.

12.3.2.5 Adverse effects, drug interactions and contraindications

Describe the principal adverse effects and contraindications of the drugs in each class.
Discuss drug-drug, drug-food, and drug-disease interactions of each drug.
Explain how concomitant use of NSAIDS, e.g., ibuprofen, can interfere with the antiplatelet actions of aspirin.
Contrast the effects of reversible with irreversible inhibitors on duration of action.

12.3.2.6 Therapeutic uses

Discuss the approach to the management of the patient on short-term and long-term antiplatelet therapy.
Explain the role of the platelet glycoprotein IIb/IIIa inhibitors in the diagnosis and management of coronary artery disease.
Contrast the effects of aspirin, dipyridamole, clopidogrel, and propranolol for primary post MI prophylaxis.
Compare differences and similarities in appropriate clinical indications for antiplatelet agents.

12.3.2.7 Clinical Pharmacology

Low-dose enteric-coated aspirin is now considered standard of care to prevent recurrence of a myocardial infarction. In patients with atrial fibrillation and one or more additional risk factors, warfarin was found superior to clopidogrel plus aspirin for stroke risk reduction (ACTIVE W Trial). In selected patients with CHF in normal sinus rhythm warfarin has no advantage over aspirin for stroke risk reduction (WARCEF trial). It is important to emphasize to patients receiving low-dose enteric-coated aspirin either prophylactically or post-myocardial infarction that concurrent NSAIDs for pain management are contraindicated, and that acetaminophen becomes the first-choice non-opioid analgesic for initial pain management.

12.3.2.8 Relevance

USMLE topic	**Principles of therapeutics**
Hematopoietic and Lymphoreticular Systems-Abnormal Processes-Hemorrhagic and Hemostatic Disorders	Anti-platelet drugs
AAMC Medical School Objectives Project Report X Patient Safety – Table 1	**Topic C:** Drug treatment of common conditions, **Topic D:** Management of less common but severe medical conditions and emergencies.

Notes

The anti-inflammatory, analgesic, and antipyretic effects of aspirin and NSAIDs, including COX-2 inhibitors, are discussed in the Autacoids Section (9).

12.4 Thrombolytic Drugs	
Recommended Curriculum Equivalent: 0.25 hr	
12.4.1 Drug Classes and Drugs	
Plasminogen Activators	Inhibitors of Fibrinolysis
t-PA ALTEPLASE reteplase tenectaplase	aminocaproic acid
12.4.2 Content Recommendations	
12.4.2.1 Physiology and pathophysiology Explain the role of plasminogen in thrombolysis. Describe the role of thrombolysis in the physiology of hemostasis.	
12.4.2.2 Mechanism of action Contrast the molecular mechanism and site of action of alteplase with aminocaproic acid. Describe the pharmacologic effects of alteplase on thrombi.	
12.4.2.3 Pharmacokinetics Differentiate between the pharmacokinetic properties of t-PA, alteplase and tenecteplase.	
12.4.2.4 Adverse effects, drug interactions and contraindications Relate the major adverse effect of thrombolytic drugs to their mechanism of action. Describe the primary contraindications for thrombolytic drugs.	
12.4.2.5 Therapeutic uses Identify the major indications for thrombolytic drug therapy: Myocardial infarction Ischemic stroke Deep venous thrombosis Pulmonary embolism Discuss aminocaproic acid (EACA), a fibrinolytic inhibitor, which is used routinely along with desmopressin and factor replacement in dental procedures in patients with hemophilia and von Willebrand's disease and for non-dental bleeding episodes in both diseases.	
12.4.2.6 Clinical Pharmacology The plasminogen activator thrombolysis drugs have been studied almost exclusively in acute myocardial infarction patients. These fibrin-specific agents are perceived to be associated with a lower all-cause mortality than the nonspecific thrombolytic drug streptokinase. These drugs are still considered too new to determine their ultimate utility for other thrombotic disorders, and whether or not adverse events are drug class-specific or a reflection of differences among competing marketed products.	

12.4.2.7 Relevance	
USMLE topic Hematopoietic and Lymphoreticular Systems-Abnormal Processes-Hemorrhagic and Hemostatic Disorders	**Principles of therapeutics** thrombolytic drugs
AAMC Medical School Objectives Project Report **X Patient Safety –** Table 1	**Topic C:** Drug treatment of common conditions **Topic D:** Management of less common but severe medical conditions and emergencies.

13.TOXICOLOGY AND THERAPY OF INTOXICATION

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13.1 Introduction to Toxicology and Therapy of Intoxication

A medical pharmacology course should be primarily concerned with three aspects of toxicology: adverse effects of therapeutic agents, acute intoxications, and chronic poisoning/environmental toxicology. The adverse effects of drugs should be taught along with the pharmacology of individual drugs or groups of drugs.

The discussion of acute intoxications should constitute a short, but important, part of the pharmacology course and should deal with the techniques and procedures used in dealing with the effects of exposure to acutely toxic materials. Lectures dealing with chronic intoxications should emphasize environmental toxicology and risk assessment.

13.2 Principles of Toxicology

Recommended Curriculum Equivalent: 1 hr

13.2.1 Content Recommendations

Describe how toxicants are influenced by the basic pharmacokinetic and pharmacodynamic processes such as absorption, distribution, biotransformation, excretion and cellular targets.

Explain the principles of bioactivation of chemicals to toxic species.

Describe the concept of dose-response curves and how it can be helpful in the management of acute and chronic poisonings.

Explain the concepts of threshold levels for toxicity.

Describe measures for determining the safety of a drug or non-therapeutic chemical (e.g. therapeutic ratio).

Explain how toxicogenetics can alter responses to chemicals

13.3 Priority Toxic Chemicals	
Recommended Curriculum Equivalent: 2 hr	
13.3.1 Drugs, Chemical Toxicants & Antidotes	
Acetaminophen Benzodiazepines Beta-blockers Opioids (Heroin, morphine) Salicylates	METALS Arsenic Beryllium Cadmium Iron Lead Mercury
ANTIDOTES Activated Charcoal Acetaminophen Benzodiazepines Beta-blockers Opioids (Heroin, morphine) Salicylates ANTIDOTES Activated Charcoal Atropine/2-PAM Ethanol Flumazenil Fomepizole Metal Chelators Methylene Blue N-Acetyl-L-Cysteine Naloxone Pralidoxime Physostigmine AIR POLLUTANTS Carbon Monoxide Sulfur Dioxide Nitrogen Dioxide Ozone ALCOHOLS Ethanol Methanol Ethylene Glycol ENVIRONMENTAL POLLUTANTS Asbestos Endocrine Disruptors Polychlorinated & Polybrominated Biphenyls Perfluorinated Compounds HERBICIDES	METALS Arsenic Beryllium Cadmium Iron Lead Mercury METAL CHELATORS Edetate Calcium Disodium Ethylenediamine Tetraacetic Acid (EDTA) Deferoxamine, Deferiprone, Deferasirox Dimercaprol Dimercaptosuccinic acid (Succimer) Penicillamine Prussian Blue Unithiol PESTICIDES Botanical Pesticides Organophosphate Carbamates Sodium bicarbonate Glucagon Oxygen Sodium or amyl nitrite/sodium Thiosulfate SOLVENTS Halogenated Aliphatic Hydrocarbons Aromatic Hydrocarbons Polychlorinated Biphenyls (PCBs)

Chlorophenoxy Herbicides (2,4-D & 2,4,5-T) Glyphosate Bipyridyl Herbicides (Paraquat) Cyanide	

13.3.2 Content Recommendations

Explain how exposure to toxicants can occur.
Describe the signs and symptoms of a toxic exposure induced by each of the toxicants.
Describe the mechanism of toxicity of toxicants.
Compare and contrast the toxicity induced by various metals.
Compare and contrast the toxicity induced by the neurotoxic pesticides.
Compare and contrast the toxicity induced by environmental compounds.
Compare and contrast the toxicity induced by certain alcohols and medications.
Describe the antidote and/or treatment for each toxicant.

13.4 Management of Acute Intoxications

Recommended Curriculum Equivalent: 1 hr

13.4.1 Content Recommendations

This section can be case-based to follow up on the identification of priority toxicant poisoning and the therapeutic aspects of treating intoxications.

Alternatively, lectures can be provided to teach the "decision-tree" approach to the treatment of acute intoxications using examples such as acetaminophen overdose.

Explain the basic principles of managing an acute intoxication from a drug or non-drug.

Describe how decisions are made to determine how an acute intoxication should be handled.

Define what is a toxidrome and know the main signs and drugs/toxins that are associated with the anticholinergic, sympathomimetic and cholinergic toxidromes.

Describe common intoxications and their management.

Define a Poison Control Center and services and information it can provide to physicians.

13.4.2 Clinical Pharmacology

For salicylate overdose, acetazolamide is only to be considered as an intervention with failure to alkalinize the urine after intravenous doses of bicarbonate.

CAUTION:
Serum potassium must be carefully monitored to limit the potential for cardiac arrhythmias. Glucose is also to be administered to counter the uncoupling of mitochondrial oxidative phosphorylation by circulating salicylic acid.
Syrup of ipecac is no longer recommended as a home remedy for pediatric intoxications, since its emetic action is not effective to remove clinically relevant amounts of dosage forms in the time period after the ingestion when it is likely to be administered. Its acute sedative effect may increase the risk of aspiration pneumonia.
Activated charcoal is not effective as an antidote for drug overdose in patients appearing at Emergency Departments, since its efficacy has only been demonstrated within 2 hours of the toxic ingestion. Almost no overdose patients ever appear for treatment within this time interval.

Tabular Information on Antidotes	
13.4.3.1 Drug/Chemical Toxicant	13.4.3.2 Antidote/Therapy
Acetylcholinesterase Inhibitors: Organophosphates	Atropine/Pralidoxine (2-PAM)
Benzodiazepines	Flumazenil
Opioids (Heroin, Morphine, others)	Naloxone, Naltrexone, Buprenorphine, Methadone
Acetaminophen	N-Acetyl-Cysteine (NAC)
Salicylate	Sodium Bicarbonate (Alkalinize the urine)
Methanol/Ethylene Glycol	Ethanol
Ethanol	Disulfiram, Acamprosate, Naltrexone
Beta-blockers	Glucagon
Cyanide (CN)	Sodium nitrite/ Sodium thiosulfate

13.4.3 General Antidotes	
Activated Charcoal	N-Acetyl-Cysteine
Atropine /2-PAM	Naloxone
Ethanol	Pralidoxime
Flumazenil	Physostigmine
Fomepizole	Sodium bicarbonate
Metal Chelators	Oxygen
Methylene Blue	

13.4.4 Heavy Metals	
Metals	Chelators *
Arsenic Beryllium Cadmium Copper Iron Lead Mercury	Deferoxamine, Deferiprone, Deferasirox Dimercaprol Dimercaptosuccinic acid (Succimer) Edetate Calcium Disodium Ethylenediamine Tetraacetic Acid (EDTA) Penicillamine Prussian Blue Unithiol

*Metals do not correspond to the adjacent chelators

Pollutants	Agricultural Chemicals	Alcohols	Solvents

Environmental	Air	Herbicides	Pesticides	Ethanol	Halogenated Aliphatic Hydrocarbons (HAC)
Polychlorinated & Polybrominate Biphenyls (PCBs)	CO	Chlorophenoxy Acids	Chlorinated Hydrocarbons	Methanol	Aromatic Hydrocarbons
Dioxins	NO_2	Glyphosate	Cholinesterase inhibitors	Ethylene Glycol	Hydrocarbons
Asbestos	O_3	Bipyridyl (Paraquat)	Botanicals		
Endocrine Disruptors	SO_2		Carbamates		
Metals	CN		Organochlorines		
Perfluorinated Compounds			Organophosphates		

13.5 Environmental Toxicology/Risk Assessment

Recommended Curriculum Equivalent: 1 hr

13.5.1 Content Recommendations

Explain the concept of risk versus dose and methods for risk assessment.
Describe the concept of pre-carcinogens, proximate carcinogens and ultimate carcinogens.
Describe bioactivation pathways for xenobiotics.
Describe the mechanisms of action for adverse effects associated with xenobiotics .
Differentiate between mutagenicity and carcinogenicity.
Describe preventive mechanisms from xenobiotic adverse effects.
Describe how toxicogenomic studies may be used to identify potential modes of action and/or bioactivation for a chemical and determine across species for use in risk assessment.

13.6 Relevance

USMLE topic General Principles – Pharmacodynamic and pharmacokinetic processes	**Principles of therapeutics** Mechanisms of action and use of drugs for treatment of toxic overdose
AAMC Medical School Objectives Project Report X Patient Safety – Table 1 **Contemporary Issues in Medicine: Basic Science and Clinical Research**	**Topic B:** Principles of clinically important pharmacokinetics **Topic C:** Drug treatment of common conditions **Topic D:** Management of less common but severe medical conditions and emergencies **Basic Science Education: Medical School Objectives**

14. VITAMINS, NATURAL PRODUCTS, AND HERBALS

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Recommended Curriculum Equivalent: 0.75 hr

14.1 Natural Products to consider

BITTER ORANGE/EPHEDRA
ECHINACEA
FISH OIL/KRILL OIL
GARCINIA CAMBOGIA
GINGER
GIN KGO
GINSENG
GLUCOSAMINE CHONDROITIN
GREEN TEA
GUARANA
MELATONIN
SAW PALMETTO
ST JOHN'S WORT
TURMERIC/CURCUMIN

Alpha-lipoic acid
Aloe vera
Black cohosh
Biotin
Caffeine, theobromine
Chamomile
Cinnamon
DHEA
Feverfew
Kava
Milk thistle
MSM (Methylsulfonylmethane) Resveratrol
SAM-e
Valerian
Yohimbe

14.1.1 Content Recommendations

14.1.1.1 Physiology and pathophysiology
Describe the physiological targets of each of the products listed above.

14.1.1.2 Mechanism of action
Describe the mechanism of action of each herbal product and identify
those that are similar to those of prescription medications, (e.g., bitter orange/synephrine, Saw Palmetto blocking testosterone, St. John's Wort inhibiting 5-HT reuptake and MAO).
Identify herbal products that have demonstrated effectiveness
Identify herbal products that are not considered to be effective for the purposes for which they are promoted.

14.1.1.3 Actions on organ systems
Describe the effects of each herbal product on various organ systems.

14.1.1.4 Pharmacokinetics
Identify mechanisms of absorption and elimination of each drug.

14.1.1.5 Adverse Effects, drug interactions and contraindications
Identify adverse effects on organ systems, including
Liver: Asian ginseng, black cohosh, kava, valerian
Kidney: Aloe vera, echinacea, ephedra
Cardiovascular system: bitter orange/ephedra, caffeine and theobromine.

Identify serious drug interactions of herbal products, including:

- Bitter orange with MAOIs
- Ginkgo with anticoagulants

- St John's Wort with protease inhibitors, calcineurin inhibitors, oral contraceptives, antidepressants, general anesthetics, digoxin, warfarin, phenytoin
- Yohimbe with clonidine, MAOIs, tricyclic antidepressants and phenothiazines
- Garcinia cambogia with hypoglycemic medications and statins, and warfarin

Describe other adverse effects including allergy (chamomile, echinacea, milk thistle, feverfew, gingko), increased blood pressure and possible stroke (bitter orange, ephedra), liver damage (concentrated green tea extracts, garcinia cambogia, kava).

Identify herbal products that are contraindicated in pregnancy.

14.1.1.6 Therapeutic Uses

Saw palmetto is marginally effective for benign prostatic hyperplasia.
Melatonin may be useful to reduce jet lag.
St Johns Wort may be effective in mild depression.
Ginger may be useful for nausea.
Glucosamine chondroitin may reduce knee pain.
Curcumin may have anti-inflammatory effects.

Notes

There is little FDA oversight for vitamins that are taken orally so that the purity and quantity may vary from one product to another.

Biotin may interfere with measurement of thyroid stimulating hormone by immunoassay.

There is little regulation of herbal products and nutraceuticals, and although FDA does try to remove fraudulent and unsafe products, there is no guarantee that the labeling is accurate.

Herbal products have been contaminated with prescription drugs as well as heavy metals and drugs banned in the US.

15. IMMUNOPHARMACOLOGY

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15.1 ANTI-INFLAMMATORY AGENTS (excluding Corticosteroids)		
Recommended Curriculum Equivalent:1 hr		
15.1.1 Drug Classes and Drugs		
SALICYLATES	**COX1/2 INHIBITORS**	**LEUKOTRIENE MODIFIERS**
ASPIRIN SULFASALAZINE MESAMYLAMINE	IBUPROFEN NAPROXEN INDOMETHACIN, KETOROLAC Diclofenac MELOXICAM CELECOXIB	Zileuton MONTELUKAST Zafirlukast
15.1.2 Content Recommendations		
15.1.2.1 Physiology and pathophysiology Delineate the pharmacologic interventions in eicosanoid pathways in the management of pain, inflammation, cardiovascular/pulmonary disorders and reproduction.		
15.1.2.2 Mechanism of action Distinguish the mechanism of action for each drug class and the differential target(s) of each agent in resolution of inflammation.		
15.1.2.3 Actions on organ systems Compare and contrast the effect and selectivity of individual agents on differential physiologic targets and the relationship of these effects in the treatment of inflammatory disorders of specific organs.		
15.1.2.4 Pharmacokinetics Specify key pharmacokinetic parameters of agents within a drug class, including the routes of administration, in relation to differential treatment paradigms.		
15.1.2.5 Adverse effects, drug interactions and contraindications List the major acute and chronic toxicities associated with each agent and/or class. Identify patient populations in which these agents should not be used.		
15.1.2.6 Therapeutic uses Identify the use of a particular anti-inflammatory class/agent in the treatment of organ specific inflammatory disorders.		
Notes Identify organ-specific toxicities (*e.g.*, GI ulceration) elicited by these agents.		

15.2 CORTICOSTEROIDS

Recommended Curriculum Equivalent: 1 hr

15.2.1 Drugs

GLUCOCORTICOIDS	CORTICOSTEROID SYNTHESIS INHIBITORS	CORTICOSTEROID RECEPTOR ANTAGONISTS
Beclomethasone Cortisone and hydrocortisone Dexamethasone Methylprednisolone Prednisone Triamcinolone	Ketoconazole	Mifepristone Spironolactone

15.2.2 Content Recommendations

15.2.2.1 Physiology and pathophysiology

Identify the adrenal regions responsible for the synthesis and secretion of mineralocorticoid, glucocorticoids (GCs) and adrenal androgens

Recognize glucocorticoid biosynthetic pathway as a target for corticosteroid synthesis inhibitors

Describe the regulation of corticosteroid synthesis by ACTH and feedback inhibition.

15.2.2.2 Mechanism of action

Explain the molecular mechanism of action of agonists and antagonists in each drug class.

Recognize receptor-independent effects via 11-beta-steroid hydroxylase on corticosteroid specificity.

15.2.2.3 Actions on organ systems

Describe the actions of corticosteroids on intermediary metabolism, growth and development, electrolyte homeostasis, immune and inflammatory responses.

Discuss the cellular/molecular mechanisms of action of corticosteroids.

Discuss the importance of synthetic glucocorticoids, especially those modifications that enhance pharmacodynamic activity and/or determine activity based on route of administration.

15.2.2.4 Pharmacokinetics

Describe the significance of corticosteroid disposition (protein binding, biotransformation, enzyme induction) that may necessitate changes in dosage regimens and routes of administration.

15.2.2.5 Adverse effects, drug interactions and contraindications

List the adverse effects/contraindications related to corticosteroid use.

Distinguish between adverse effects observed with short versus chronic glucocorticoid use.

15.2.2.6 Therapeutic uses

Explain the rationale for corticosteroid use in replacement therapy, as anti-inflammatory and immunosuppressive agents, and as diagnostic agents in hypothalamo-pituitary adrenocortical disease/dysfunction.

Explain the rationale for slow withdrawal following chronic therapy with glucocorticoids.

Discuss the rationale for spironolactone in treating primary hyperaldosteronism.

Explain the roles of mifepristone in managing the symptoms associated with Cushing syndrome

Notes

Prednisone is a prodrug and may be poorly activated in patients with severe liver disease.

Ketoconazole is a potent inhibitor of both CYP3A4 and P-glycoprotein. It is to be used with caution in patients receiving other drug therapies that are modulated by this transporter (P-gp) and drug metabolizing enzyme (3A4).

15.3 CYTOTOXIC AGENTS

Recommended Curriculum Equivalent: 0.5 hr

15.3.1 Drug Classes and Drugs

Antimetabolites	**Inhibitors of purine synthesis**	**Alkylating Nitrogen mustards**
AZATHIOPRINE METHOTREXATE	MYCOPHENOLATE MOFETIL	CYCLOPHOSPHAMIDE

15.3.2 Content Recommendations

15.3.2.1 Physiology and pathophysiology

Describe the role of inappropriate immune cell function and dysregulation of the immune system leading to chronic inflammation, organ transplant rejection, and organ-specific diseases such as IBD, psoriasis, and rheumatic diseases.

15.3.2.2 Mechanism of action

Distinguish the mechanism of action of each drug class and the differential target of each agent in mediating immunosuppression and inhibiting lymphocyte proliferation and function.

15.3.2.3 Actions on organ systems

Compare and contrast the actions(s) of each drug class on immune cell function leading to immunosuppression.

15.3.2.4 Pharmacokinetics

Specify key pharmacokinetic parameters of agents within a drug class, including the route of administration, in relation to differential treatment paradigms.

15.3.2.5 Adverse effects, drug interactions and contraindications

List the major acute and chronic toxicities associated with each agent/class, and the cautious or prohibitive use of a drug class or specific agent.

Identify agents contraindicated in pregnancy.

15.3.2.6 Therapeutic uses

Identify the selective use of each pharmacotherapeutic agent, as it relates to the mechanism of action of the drug, in the treatment of organ-specific inflammatory disorders and/or prevention of organ transplant rejection.

Notes

Identify organ-specific toxicities elicited by these agents.

15.4 CYTOKINE MODULATORS AND INHIBITORS

Recommended Curriculum Equivalent: 2 hr

15.4.1 Drug Classes and Drugs

Cytokine modulators INTERFERON α, β, γ BASILIXIMAB	**Calcineurin Inhibitors** CYCLOSPORINE TACROLIMUS	**Interleukin Inhibitors** Anakinra Mepolizumab/Resilizumab BENRALIZUMAB TOCILIZUMAB Ustekinumab
Janus kinase inhibitors TOFACITINIB	**MTOR Inhibitors** SIROLIMUS Everolimus	**TNFalpha Inhibitors** INFLIXIMAB ETANERCEPT ADALIMUMAB

15.4.2 Content Recommendations

15.4.2.1 Physiology and pathophysiology

Describe the role of cytokines in the immune response and the dysregulation of cytokine secretion and immune cell function in the setting of viral infection, specific immune disorders and organ transplant rejection.

15.4.2.2 Mechanism of action

Compare and contrast the actions(s) of each drug class/agent in modulating the immune system resulting in activation of immune cell function (interferons) and immunosuppression.

15.4.2.3 Actions on organ systems

Distinguish the effect of specific agents on their differential physiologic targets and the relationship of these interactions in the attenuation of an exaggerated organ specific inflammatory response, regulation of T-cell activation, phagocyte activation and downregulation of viral/bacterial protein synthesis.

15.4.2.4 Pharmacokinetics

Specify key pharmacokinetic parameters of agents within a drug class, including the route of administration, in relation to differential treatment paradigms.

15.4.2.5 Adverse effects, drug interactions and contraindications

List the major acute and chronic toxicities associated with each class/agent, and the cautious or prohibitive use of a drug class or specific agent.

Identify agents contraindicated in pregnancy

Identify underlying disease states which would necessitate alternative therapy

Describe the potential for the patient to develop/reactivate neoplasm or infectious diseases when treated with these agents

15.4.2.6 Therapeutic uses

Identify the use(s) of a particular agent in each class in the treatment of immune disorders, e.g., organ transplant rejection: basiliximab (IL-2), calcineurin and MTOR inhibitors; musculoskeletal rheumatic diseases & inflammatory bowel disease: TNFα inhibitors and JAK inhibitors; musculoskeletal dermatologic, and rheumatic diseases & arteritis: interleukin inhibitors; hepatitis antiviral activity: interferons α, β; immune cell activation (chronic granulomatous disease): interferon γ

Notes

Identify organ-specific toxicities elicited by these agents.

Discuss the management of potential severe reactions resulting from treatment with these agents.

15.5 DRUGS PRODUCING T-CELL DEPLETION

Recommended Curriculum Equivalent: 0.25 hr

15.5.1 Drug Classes and Drugs

Co-stimulation inhibitors	Immunoglobulins
BELATACEPT ALEMTUZUMAB	Antilymphocyte globulin (ALG) Antithymocyte globulin (ATG)

15.5.2 Content Recommendations

15.5.2.1 Physiology and pathophysiology

Describe the physiology of T-cell activation including the role of co-stimulation receptors.

Explain how the co-stimulation receptors can be used to deplete T-cells.

Describe the therapeutic applications for depletion of T-cells.

15.5.2.2 Mechanism of action

Describe the mechanism of action of the drugs on the various targets.

15.5.2.3 Actions on organ systems

Describe the effects of each drug on various types of blood cells, joints, CNS, and heart.

15.5.2.4 Pharmacokinetics

Identify types of administration and factors affecting metabolism and elimination

15.5.2.5 Adverse effects, drug interactions and contraindications

Discuss the risk of serious infections in patients receiving these drugs and consider the need for prophylaxis against common opportunistic infections.

Describe the risk of inducing leukopenia, lymphopenia or other malignancies with use of these drugs.

Recognize the risk of infusion reactions and serious hypersensitivity reactions with ATG, ALG and alemtuzumab.

15.5.2.6 Therapeutic uses

Identify the therapeutic uses of these drugs in preventing or rescuing organ transplant or for stem cell transplant.

Notes

Belatacept is only used in patients who are Epstein Barr positive due to the risk of post-transplant lymphoproliferative disorder in those who are seronegative. Consider prophylaxis for cytomegalovirus, herpes, and *P. jiroveci* in patients treated with this drug.

15.6 IMMUNE CHECKPOINT INHIBITORS

Recommended Curriculum Equivalent: 0.5 hr

15.6.1 Drug Classes and Drugs

ANTI-CTLA-4	ANTI-PD1/PD-L1	LAG-3 INHIBITORS	Bispecific CD19-directed CD3 T cell engager
Ipilimumab	Nivolumab Pembrolizumab Atezolizumab	Relatlimab	Blinatumomab

15.6.2 Content Recommendations

15.6.2.1 Physiology and pathophysiology

Discuss the activation and regulation processes of immune system and potential impacts on health when the processes are dysregulated. Describe the role of checkpoint proteins and delineate key checkpoint pathways e.g., PD-1/PD-L1 and CD28/CTLA-4 pathways and the pharmacologic interventions in cancers.

15.6.2.2 Mechanism of action

Describe the mechanism of action for each drug class in and identify specific target(s) of each agent.

15.6.2.3 Actions on organ systems

Describe the pharmacological effects of the drugs in each class on the immune system. Compare and contrast the effect of each immune checkpoint inhibitor on T cells, and the relationship of these effects in the treatment of hematologic as well as solid tumors.

15.6.2.4 Pharmacokinetics

Specify key pharmacokinetic parameters of agents within a drug class, including the route of administration, and catabolism and elimination of antibody drugs.

15.6.2.5 Adverse effects, drug interactions and contraindications

List the major acute and chronic toxicity associated with each agent and/or class such as infusion reaction and immune-related adverse events.

15.6.2.6 Therapeutic uses

Differentiate the use of these drugs in hematologic malignancies and solid tumors.

Notes

Discuss the management of potential severe reactions due to over-activation of the immune system.

15.7 MISCELLANEOUS AGENTS

Recommended Curriculum Equivalent: 1 hr

15.7.1 Drug Classes and Drugs

ANTI-LFA-3 ANTIBODIES ALEFACEPT	**IMMUNE GLOBULIN INTRAVENOUS** IGIV	**ANTI-INTEGRIN ANTIBODIES** NATALIZUMAB VEDOLIZUMAB	**TOLL-LIKE RECEPTOR ACTIVATORS** IMIQUIMOD
CTLA-4-Ig ABATACEPT BELATACEPT	**B CELL DEPLETION** Obinutuzumab Ocrelizumab		**Immunizing Agents** Rho(D) immune globulin

15.7.2 Content Recommendations

15.7.2.1 Physiology and pathophysiology

Review the physiological functions of membrane glycoproteins and factors participating in immune cell function.

Describe the involvement of immune cells in pathophysiology of different disease states.

Discuss the effects of IGIV on modulation of immune function in different pathological states

15.7.2.2 Mechanism of action

Distinguish the mechanism of action for each drug class and the differential target(s) of each agent in modulating immune-mediated disorders e.g., psoriasis, autoimmune disorders, Crohn disease, genital warts, and myeloma.

15.7.2.3 Actions on organ systems

Compare and contrast the effect and selectivity of individual agents on the differential physiologic target, and the relationship of these effects in the treatment of inflammatory disorders of specific organs.

15.7.2.4 Pharmacokinetics

Specify key pharmacokinetic parameters of agents within a drug class, including the route of administration, catabolism and elimination.

15.7.2.5 Adverse effects, drug interactions, and contraindications

List the major acute and chronic toxicity associated with each agent and/or class such as infusion reaction and immune-related adverse events.

15.7.2.6 Therapeutic uses

Delineate pharmacologic treatment options for organ specific immune-mediated disorders.

15.8 DRUGS FOR THE TREATMENT OF RHEUMATIC DISEASES

Recommended Curriculum Equivalent: 1 hr

15.8.1 Drug Classes and Drugs

Adjunct Therapies	DMARDS (Disease Modifying Antirheumatic Drugs)		
	Biologics	**JAK Inhibitors**	**Conventional Therapies**
IBUPROFEN CELECOXIB Glucocorticoids	ETANERCEPT ADALIMUMAB Infliximab Tocilizumab RITUXIMAB	TOFACITINIB	METHOTREXATE Leflunomide Hydroxychloroquine Sulfasalazine

15.8.2 Content Recommendations

15.8.2.1 Physiology and pathophysiology

Recognize that rheumatoid arthritis is a systemic, chronic inflammatory disease characterized by destructive synovitis.

Describe the role of inflammatory mediators, especially TNF-□ and IL-6, in the progression of joint destruction

15.8.2.2 Mechanism of action

Explain the molecular mechanism of action common to all nonsteroidal anti-inflammatory drugs (NSAIDs).

Describe the proposed mechanisms of the antirheumatic action of DMARDs.

15.8.2.3 Actions on organ systems

Describe the actions of these agents on immune function.

Recognize the effects of these agents on eye, kidney, liver, musculo skeletal system, and reproduction.

15.8.2.4 Pharmacokinetics

Recognize the time required before the onset of action of the DMARDs.

15.8.2.5 Adverse effects, drug interactions and contraindications

Describe the main adverse effects of the drugs of each class.

Describe the clinically important drug interactions of the drugs of each class.

Describe the principal contraindications or precautions of the drugs of each class.

Identify the agents contraindicated in pregnant patients and those with preexisting liver disease

Identify the symptoms of the rituximab hypersensitivity reaction, discuss the underlying pathology and develop a plan to treat the patient undergoing this reaction

15.8.2.6 Therapeutic uses

List the other inflammatory conditions for which DMARDs have demonstrated utility.

Notes

Recognize that DMARD therapy should begin as soon as a diagnosis of RA is made.

Treatment should be tailored to the severity of the disease.

NSAIDs and low dose corticosteroids may be used to control symptoms during flares.

15.9 DRUGS USED FOR TREATMENT OF MULTIPLE SCLEROSIS

Recommended Curriculum Equivalent: 0.25 hr

15.9.1 Drug Classes and Drugs

MONOCLONAL ANTIBODIES	PYRIMIDINE SYNTHESIS INHIBITOR	Class II MHC suppression	MBP decoy	ANTI-IMFLAMMATORY
NATALIZUMAB OCRELIZUMAB Alemtuzumab	Teriflunomide Leflunomide	Interferon 1-beta	Glatiramer	Fingolimod Dimethyl fumarate

15.9.2 Content Recommendations

15.9.2.1 Physiology and pathophysiology

Describe the pathology involved in myelin destruction in multiple sclerosis.

15.9.2.2 Mechanism of action

Differentiate the mechanism of action of each drug class.

15.9.2.3 Actions on organ systems

Relate the effects of each drug on the immune system and/or on myelin with respect to efficacy in suppressing inflammation and demyelination.

15.9.2.4 Pharmacokinetics

Identify types of administration and factors affecting metabolism and elimination.

15.9.2.5 Adverse effects, drug interactions and contraindications

Identify the agents most likely to induce progressive multifocal leukoencephalopathy (PML) and patient characteristics which heighten this risk.

Describe other drug-specific adverse effects that may occur.

Identify drugs that are teratogenic.

15.9.2.6 Therapeutic uses

Identify drugs of first choice based on effectiveness and minimal serious side effects.

Note

Recognize that a history of JC virus infection increases the patient's risk of developing PML.

16. ANTIMICROBIAL DRUGS

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Basic Principles of Antimicrobial Therapy
Recommended Curriculum Equivalent: 1 hr
16.1 Introduction
16.1.1 Content Recommendations
Define the terms: antibiotics, selective toxicity, therapeutic index, bacteriostatic and bactericidal, chemotherapeutic spectrum. Understand the MIC and MBC values. Describe the terms synergism and antagonism. Discuss the classification of antimicrobial drugs based upon the mechanism of action. Explain the modes of action of various antimicrobial drugs. Define bacterial resistance and illustrate the mechanisms involved in acquiring bacterial resistance. Describe the basic principles of combination therapy with antimicrobial drugs.

16.2 Cell Wall Synthesis Inhibitors and Cell Membrane Active Agents
Recommended Curriculum Equivalent: 2 hr
16.2.1 Drug Classes and Drugs

16.2.1.1 Cell Wall Synthesis Inhibitors			
Beta-lactams			Others
Penicillins	Cephalosporins	Carbapenems	
PENICILLIN G penicillin V OXACILLIN dicloxacillin nafcillin AMPICILLIN +/- Sulbactam AMOXICILLIN +/- CLAVULANATE PIPERACILLIN + TAZOBACTAM ticarcillin+/- clavulanate	CEPHALEXIN cefazolin CEFUROXIME cefotetan cefoxitin CEFTRIAXONE cefotaxime ceftazidime CEFEPIME cefiderocol CEFTAROLINE	IMIPENEM + CILASTATIN MEROPENEM Doripenem	VANCOMYCIN Dalbavancin* Telavancin* Teicoplanin Bacitracin Fosfomycin
		Monobactams	
		AZTREONAM	

16.2.1.2 Cell Membrane Active Agents
DAPTOMYCIN COLISTIN Polymyxin B (drugs marked with * from sections above may also have cell membrane activity)

16.2.2 Content Recommendations
16.2.2.1 Mechanism of action Describe the mechanism of action of β-lactam antibiotics Understand the principle of combination of inhibitors of β-lactamase with penicillins (List such combinations). Explain the pharmacological basis for combining imipenem with cilastatin. Describe the mechanism of action of non-beta-lactam cell wall synthesis inhibitors and cell membrane active agents Describe the five generations of cephalosporins with specific examples and the differences in their antimicrobial spectrum
16.2.2.2 Pharmacokinetics Describe the effect of probenecid on penicillin and vancomycin elimination. Describe the repository penicillins. Explain the use of imipenem with cilastatin.
16.2.2.3 Adverse effects and contraindications Identify common and serious adverse effects of the drugs listed above, e.g. bacitracin-associated nephrotoxicity. Explain the terms superinfection and cross-hypersensitivity.
16.2.2.4 Therapeutic uses Compare the anti-bacterial spectrum and uses of different beta-lactams. Discuss the uses of vancomycin in Anthrax, Clostridial, Corynebacterium, Enterococcal, Pneumococcal, Staphylococcal and Streptococcal infections. Discuss the uses of different cell membrane-active agents in either Gram-positive or Gram-negative infections. Describe the use of topical bacitracin in Gram-positive infections. Describe the uses of fosfomycin in urinary tract infections.

16.2.2.5 Clinical Pharmacology: Vancomycin use should be reserved for treatment of MRSA infections. Carbapenems and 3rd and 4th generation cephalosporin antibiotics should be reserved for patients with very serious polymicrobial infections. Carbapenems can reduce the serum concentration of valproate, leading to recurrence of seizures.

16.3 Protein Synthesis Inhibitors

Recommended Curriculum Equivalent: 1.5 hr

16.3.1 Drug Classes and Drugs

Aminoglycosides	Macrolides	Streptogramins
GENTAMICIN amikacin neomycin streptomycin tobramycin	AZITHROMYCIN CLARITHROMYCIN ERYTHROMYCIN	QUINUPRISTIN/DALFOPRISTIN
Lincosamides	**Oxazolidinones**	**Tetracyclines**
CLINDAMYCIN	LINEZOLID tedizolid	DOXYCYCLINE TIGECYCLINE minocycline tetracycline
Others		
MUPIROCIN chloramphenicol		

16.3.2 Content Recommendations

16.3.2.1 Mechanism of action

Discuss the mechanism of action of each class of protein synthesis inhibitors.

Explain the mechanism of acquired drug resistance to aminoglycosides, tetracyclines, and macrolides.

Explain the rational basis for combination therapy with an aminoglycoside and a penicillin, cephalosporin, or vancomycin.

16.3.2.2 Pharmacokinetics

Describe the pharmacokinetic properties of each class of protein synthesis inhibitors, including their routes of administration. Explain the importance of peak and trough levels of aminoglycosides.

Discuss the need of and the method of dose adjustment for aminoglycosides in patients with compromised renal function.

16.3.2.3 Adverse effects and drug interactions

Identify common and serious adverse effects of the drugs listed above, e.g. aminoglycoside-associated ototoxicity and nephrotoxicity, tetracycline-associated phototoxicity and effects on calcified tissues, and chloramphenicol-associated gray baby syndrome and aplastic anemia.

Describe the major drug interactions of macrolides due to inhibition of cytochrome P450 enzymes.

Describe the MAO inhibitory activity of linezolid.

16.3.2.4 Therapeutic uses

Compare the antibacterial spectrum and uses of different protein synthesis inhibitors.

Discuss the therapeutic options for treating skin and soft tissue infections, and systemic infections due to methicillin-resistant or vancomycin-resistant bacteria.

Describe the uses of tetracyclines in the treatment of Rickettsial infections and Lyme disease.

Describe the uses of macrolides and tetracyclines in the treatment of Chlamydia infections.

Discuss the topical uses of mupirocin.

16.3.2.5 Clinical Pharmacology

Use of macrolide antibiotics in patients receiving calcium channel blockers is associated with an increased risk of hypotension due to inhibition of CYP3A4 activity. Macrolide antibiotics also increase the risk of toxicity to statins metabolized by CYP3A4. Use of linezolid for more than 10 days is associated with bone marrow depression.

16.4 Inhibitors of Nucleic Acid Synthesis	
Recommended Curriculum Equivalent: 1 hr	
16.4.1 Drug Classes and Drugs	
Fluoroquinolones	RNA polymerase inhibitors
CIPROFLOXACIN levofloxacin moxifloxacin gemifloxacin	RIFAMPIN rifaximin FIDAXOMICIN
Nitroimidazole	Folate synthesis inhibitors
METRONIDAZOLE	COTRIMOXAZOLE (Trimethoprim-Sulfamethoxazole) [TMP-SMX]
Other Agents	
	NITROFURANTOIN
16.4.2 Content Recommendations	
16.4.2.1 Mechanism of action Explain the mechanism of action of each class of antibiotics. Discuss the synergistic inhibition due to sequential blockade with cotrimoxazole.	
16.4.2.2 Pharmacokinetics Describe the pharmacokinetics properties of each class of antibiotics. Describe the drug interactions of fluoroquinolones, including the effect of ingested cations on drug absorption.	
16.4.2.3 Adverse effects Identify common and serious adverse effects of the drugs listed above, e.g. cotrimoxazole-associated Stevens Johnson syndrome, fluoroquinolone-associated tendonitis and QT prolongation	
16.4.2.4 Therapeutic uses Describe the advantages of newer fluoroquinolones over ciprofloxacin. Describe the major therapeutic indications of cotrimoxazole. Discuss the emergence of microbial resistance to cotrimoxazole and fluoroquinolone drugs, and its implications for the treatment of urinary tract infections. Describe and compare the role of metronidazole, vancomycin, and fidaxomicin in the treatment of *Clostridioides difficile* infections.	
16.4.2.5 Clinical Pharmacology Caution in using rifampin with other drugs metabolized by CYP3A4 due to its enzyme induction property.	

16.5 Antimycobacterial Drugs

Recommended Curriculum Equivalent: 1 hr

16.5.1 Drugs

ISONIAZID	levofloxacin
RIFAMPIN	moxifloxacin
ETHAMBUTOL	cycloserine
PYRAZINAMIDE	streptomycin
RIFAPENTINE	amikacin
RIFABUTIN	kanamycin
	capreomycin
	azithromycin
	clarithromycin
DAPSONE	clofazimine
	thalidomide

16.5.2 Content Recommendations

16.5.2.1 Mechanism of action

List the first line antitubercular drugs and explain their mechanisms of action.

Define the various phases of actively and slow growing *Mycobacterium tuberculosis* and compare the relative effectiveness of various drugs.

16.5.2.2 Pharmacokinetics

Describe the pharmacokinetic profile of isoniazid and rifampin.

Describe the role of *N*-Acetyl Transferase on clinical implications in terms of therapeutic efficacy and occurrence of adverse effects of isoniazid.

16.5.2.3 Adverse effects and drug interactions

Describe the adverse effects of isoniazid, rifampin, ethambutol and pyrazinamide.

Explain the drug interactions of rifampin with anticoagulants and other drugs, such as oral contraceptives.

Describe the hematologic adverse effects of dapsone.

Describe the teratogenic effects of thalidomide.

16.5.2.4 Therapeutic uses

Describe the regimen recommended for treatment of latent tuberculosis and active tuberculosis.

Describe the mechanisms of resistance of tuberculosis bacteria on various anti tubercular drugs.

Describe the emergence of multidrug-resistant tuberculosis and its implications for the treatment of these infections.

Describe the relevance of directly observed therapy (DOT) in tuberculosis management

Discuss the use of rifampin, azithromycin and ethambutol for treatment of *Mycobacterium avium* complex.

Describe the drugs used in the treatment of leprosy and their mechanism of action.

Describe the drugs used for reversing the lepra reactions and the erythema nodosum leprosum reaction.

Explain the WHO regimen for treatment of leprosy.

16.5.2.5 Clinical Pharmacology- Mostly covered in above sections of this document.

16.6 Antiparasitic Drugs	
Recommended Curriculum Equivalent: 1 hr	
16.6.1 Drugs	
ALBENDAZOLE IVERMECTIN METRONIDAZOLE PRAZIQUANTEL	atovaquone iodoquinol mebendazole paromomycin pyrantel pamoate tinidazole nitazoxanide
16.6.2 Content Recommendations	
16.6.2.1 Mechanism of action Describe the mechanisms of action of the different antiparastic drugs.	
16.6.2.2 Therapeutic uses Identify the drug of choice for treatment of diseases due to various helminths. Identify the broad spectrum anthelmintic drugs. Identify the opportunistic infections commonly known to occur in HIV AIDS patients and the drugs used for their treatment. Identify the drugs used to treat amebiasis (differentiate between the treatment regimen for asymptomatic versus intestinal/extraintestinal disease), giardiasis, trypanosomiasis, and leishmaniasis.	

16.7 Antimalarial drugs

Recommended Curriculum Equivalent: 1 hr

16.7.1 Drugs

ARTESUNATE
ARTEMETHER/LUMEFANTRINE
CHLOROQUINE
DOXYCYCLINE
MEFLOQUINE
PRIMAQUINE
QUININE
ATOVAQUONE/PROGUANIL

16.7.2 Content Recommendations

16.7.2.1 Mechanism of action

Describe the targets of the antimalarial drugs in the life cycle of malarial parasites.
Describe the mechanisms of action of the various antimalarial drugs.
Discuss the mechanism of resistance to chloroquine.

16.7.2.2 Pharmacokinetics

Describe the pharmacokinetic properties of chloroquine.
Describe the pharmacokinetic properties and metabolism of artesunate and artemether.

16.7.2.3 Adverse effects

Explain the mechanism of hemolytic anemia induced by primaquine in G6PD deficient patients.
Describe cinchonism and the drugs causing it.
Describe the toxic effects of chloroquine.

16.7.2.4 Therapeutic uses

List the drugs of choice for treatment of uncomplicated illness and severe illness due to *P. vivax, P. ovale, P. malariae* and *P. falciparum*.
Distinguish between prophylaxis and treatment of *P. vivax, P. ovale, P. malariae*, and *P. falciparum*.
Describe the therapeutic indications for artemisinin derivatives.

16.7.2.5 Clinical Pharmacology

Drug interactions likely in patients with malaria and concurrent HIV infection due to polypharmacy and effects especially on CYP3A4 activity.

16.8 Antifungal Drugs

Recommended Curriculum Equivalent: 1 hr

16.8.1 Drugs

AMPHOTERICIN B	flucytosine
CASPOFUNGIN	ketoconazole
FLUCONAZOLE	micafungin
ITRACONAZOLE	posaconazole
VORICONAZOLE	nystatin
	terbinafine
	sulfamethoxazole-trimethoprim (cotrimoxazole)

16.8.2 Content Recommendations

16.8.2.1 Mechanism of action

Describe the mechanism of action of each class of antifungal drugs.

16.8.2.2 Pharmacokinetics

Describe the pharmacokinetic properties of the various antifungal drugs.

16.8.2.3 Adverse effects

Describe the important adverse effects of the various antifungal drugs.

16.8.2.4 Therapeutic uses

Describe the major therapeutic indications of the antifungal drugs, including current recommendations for treating aspergillosis, blastomycosis, superficial and systemic candidiasis, coccidioidomycosis, cryptococcosis, histoplasmosis and mucormycosis.

Describe the use of trimethoprim-sulfamethoxazole in the treatment of *Pneumocystis jiroveci* infections.

Discuss the appropriate duration of treatment of various fungal infections and the role of surgical debridement in treating subcutaneous mycoses.

Describe host factors that predispose patients to fungal infections.

Differentiate the azole antifungal drugs according to the route of administration.

16.8.2.5 Clinical Pharmacology

Many antifungals are strong inhibitors of CYP3A4 and caution is indicated for patients receiving concurrent drug therapy where CYP3A4 is a prominent drug metabolism pathway.

Discuss the advantages of liposomal preparations of amphotericin B.

16.9 Antiviral Drugs	
Recommended Curriculum Equivalent: 1 hr	
16.9.1 Drugs	
ACYCLOVIR FOSCARNET GANCICLOVIR OSELTAMIVIR RIBAVIRIN ENTECAVIR TENOFOVIR PEGYLATED INTERFERON ALFA NIRMATRELVIR-RITONAVIR REMDESIVIR	valacyclovir famciclovir valganciclovir cidofovir amantadine zanamivir ledipasvir-sofosbuvir sofosbuvir-velpatasvir glecaprevir-pibrentasvir
16.9.2 Content Recommendations	
16.9.2.1 Mechanism of action Classify antiviral drugs based upon their site of inhibition in the viral replication cycle. Explain the mechanism of action of each antiviral drug.	
16.9.2.2 Pharmacokinetics Compare pharmacokinetic properties of acyclovir, valacyclovir, ganciclovir, and valganciclovir.	
16.9.2.3 Adverse effects List the adverse effects and therapeutic complications of antiviral drugs. Describe potential drug interactions.	
16.9.2.4 Therapeutic uses Describe major therapeutic indications for each antiviral drugs. Compare the drugs and regimens used for prevention and treatment of cytomegalovirus infections. Describe the role and use of oseltamivir in the prophylaxis and treatment of influenza. Describe the emergence and mechanism of influenza virus resistance to amantadine. Describe the use of combination drug therapy in the treatment of hepatitis B and hepatitis C. Describe the use of nirmatrelvir-ritonavir and remdesivir in the treatment of COVID-19.	
16.9.2.5 Clinical Pharmacology In drug therapy of hepatitis, polypharmacy is the standard of care.	

16.10 Anti HIV Drugs	
Recommended Curriculum Equivalent: 1 hr	
16.10.1 Drugs	
Nucleoside Reverse Transcriptase Inhibitors (NRTI)	Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)
ABACAVIR (ABC) LAMIVUDINE (3-TC) TENOFOVIR DISOPROXIL (TDF) ZIDOVUDINE (AZT) EMTRICITABINE (FTC) didanosine stavudine	EFAVIRENZ (EFV) NEVIRAPINE (NVP)
HIV-1 protease inhibitors	Fusion Inhibitors
ATAZANAVIR (ATV) RITONAVIR (RTV) indinavir lopinavir nelfinavir saquinavir darunavir	ENFUVIRTIDE MARAVIROC
DNA Strand Transfer Inhibitor	
DOLUTEGRAVIR bictegravir raltegravir	
16.10.2 Content Recommendations	
16.10.2.1 Mechanism of action Classify anti-HIV drugs based upon their site of inhibition in the viral replication cycle. Explain the mechanisms of action of each class of anti-HIV drugs. Compare and contrast the mechanism of action of NRTIs and NNRTIs. Explain the use of combinations of drugs derived from different drug classes.	
16.10.2.2 Pharmacokinetics Explain the importance of testing for HLA-B*5701 before use of abacavir-containing regimen. Explain the importance of performing a tropism assay before use of maraviroc containing regimen. Explain the role of ritonavir and cobicistat as a pharmacokinetic boosting agent.	
16.10.2.3 Adverse effects Learn major side effects of each class of anti-HIV drugs, with emphasis on the metabolic and cardiovascular adverse effects. Describe the major drug interactions of anti-HIV drugs, with emphasis on interactions involving inhibition or induction of cytochrome P450 enzymes.	
16.10.2.4 Therapeutic uses Describe the various currently preferred drug combinations used for the treatment of HIV infections. Describe the rationale and components of once-a-day formulations for treating HIV infections. Describe the use of drugs for Pre-exposure prophylaxis (PrEP) and Post-exposure prophylaxis (PEP)	

16.10.2.5 Clinical Pharmacology

Current standard of care involves polypharmacy and almost invariably is associated with drug interactions when comorbidities are also treated with drugs. Extreme caution is advised in choosing drugs for comorbidities that may affect the elimination mechanisms of the ART drugs prescribed.

SUMMARY and DISCLAIMER

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The Editors