DRUGS ACTING ON THE CENTRAL NERVOUS SYSTEM (21)

Subcommittee:

Eisenberg, Richard, (Chair), reisenbe@d.umn.edu
Cox, Brian, bcox@usuhs.mil
Faingold, Carl, cfaingold@siumed.edu
Goldfarb, Joe, joseph.goldfarb@mssm.edu
Parkinson, Fiona E., parkins@cc.umanitoba.ca
Porrino, Linda, lporrino@wakehealth.edu
Potter, Pamela E., ppotte@midwestern.edu
Prozialeck, Walter, wprozi@midwestern.edu
Wecker, Lynn, lwecker@health.usf.edu

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 25 hours.

Neurotransmitters, Neuromodulators, and Receptors

Recommended Curriculum Equivalent: 1.5 hr

Learning Objectives

Physiology, pathophysiology and therapeutic actions

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 effector 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.

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)

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; pre- and post-synaptic receptor interactions, trophic and growth factors; brain homeostasis, blood-brain barrier	

AAMC Medical School Objectives Project Report X Patient Safety	**Topic C**

<table>
<tr><th colspan="4">General Anesthetics</th></tr>
<tr><th colspan="4">Recommended Curriculum Equivalent: 1.5 hr</th></tr>
<tr><th colspan="4">Drug Classes and Drugs to consider</th></tr>
<tr><th colspan="2">Inhalational</th><th colspan="2">Intravenous</th></tr>
<tr><td>Primary agents</td><td>Secondary agents</td><td>Primary agents</td><td>Secondary agents</td></tr>
<tr><td rowspan="3">DESFLURANE
ISOFLURANE
NITROUS OXIDE (N_2O)
SEVOFLURANE</td><td rowspan="3"></td><td>ETOMIDATE
KETAMINE
PROPOFOL</td><td>methohexital
thiopental</td></tr>
<tr><td colspan="2">Intravenous Adjuncts</td></tr>
<tr><td>FENTANYL
MIDAZOLAM
MORPHINE</td><td>alfentanil
remifentanil
sufentanil
antimuscarinic agents</td></tr>
<tr><th colspan="4">Learning Objectives</th></tr>
<tr><td colspan="4">Physiology, pathophysiology and therapeutic actions
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.</td></tr>
<tr><td colspan="4">Mechanism of action
List the current theories of the mechanisms of action of inhalation anesthetics, and of intravenous anesthetics.</td></tr>
<tr><td colspan="4">Pharmacokinetics
Compare the available inhalation anesthetics with respect to their pharmacokinetic properties including biotransformation. Explain how the solubility of a gas in a liquid is defined. List the conditions that must be specified to determine the concentration of gas in the liquid phase.
Describe how the physical properties of inhalation anesthetics influence the rate of equilibration of anesthetic in the inspired air to anesthetic in alveoli, blood, brain, muscle and fat. Explain how this information is related to onset and recovery from inhalation anesthesia.
Compare and contrast commonly used intravenous induction agents—their speed of onset, and duration of action. Describe the relative roles of distribution and metabolism in determining duration of action and how duration of action may change with repeated administration of an intravenous anesthetic.</td></tr>
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Adverse effects, drug interactions and contraindications

List and explain the complications that may ensue with the use of Nitrous Oxide as a direct result of the high concentrations at which it is administered and its solubility in blood relative to that of nitrogen.

Describe malignant hyperthermia, list some common triggering agents, and discuss its prevention and treatment.

Describe the utility and adverse effects of drugs commonly used as pre-anesthetic medications or in combination with inhalation anesthetics to create a "complete or balanced anesthetic". Include opioids, benzodiazepines, neuromuscular blocking agents and antimuscarinic agents in your discussion. Indicate how the concomitant use of these drugs may affect the concentrations of inhaled anesthetics used to maintain the anesthetic state.

Describe the pharmacological effects of the drugs in each class on pulmonary, cardiovascular, endocrine, renal, and CNS function (aside from anesthesia).

Therapeutic uses

Define MAC (minimal alveolar concentration), name the physical property of an inhalation anesthetic that correlates best with its MAC, and explain how the concept of MAC is used in anesthesiology.

Discuss relative advantages and disadvantages of intravenous vs. inhalation anesthesia.

Discuss the factors involved in choosing an anesthetic protocol, including the relative advantages and disadvantages of inhalation and intravenous anesthesia.

Clinical Pharmacology

One significant issue involves increased risk of cardiovascular mortality with propofol due to concurrent hypokalemia (increased arrhythmia risk) – this is the result of not controlling serum potassium when propofol was used as an anesthetic agent.

Relevance

USMLE topic	**Principles of therapeutics**
Central and Peripheral Nervous System	Mechanisms of action and use of drugs for treatment of disorders if the nervous system - anesthetics
AAMC Medical School Objectives Project Report X Patient Safety- Table 1	**Topic C** Drug treatment of common conditions, and diseases using frequently prescribed drugs for the treatment and prevention of disease

Local Anesthetics

Recommended Curriculum Equivalent: 1 hr

Drugs to consider

Primary agents	Secondary agents
BENZOCAINE BUPIVACAINE LIDOCAINE PROCAINE ROPIVACAINE	articaine cocaine prilocaine tetracaine

Learning Objectives

Physiology, pathophysiology and therapeutic actions

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.

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.

Mechanism of action

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

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.

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).

Clinical Pharmacology

There should be caution concerning increased cardiac morbidity and seizures if significant concentrations are achieved in the circulation.

Relevance

USMLE topic	**Principles of therapeutics**
Central and Peripheral Nervous System	Mechanisms of action and use of drugs for treatment of disorders if the nervous system – local anesthetics

AAMC Medical School Objectives Project Report X Patient Safety- Table 1	**Topic C** Drug treatment of common conditions, and diseases using frequently prescribed drugs for the treatment and prevention of disease

Opioid Analgesics, Agonist-antagonists, and Antitussives

Recommended Curriculum Equivalent: 2 hr

Drug Classes and Drugs to consider

Agonists		Agonist/Antagonists and Antagonists	
Primary	Secondary	Primary	Secondary
CODEINE FENTANYL HYDROCODONE HYDROMORPHONE METHADONE MORPHINE OXYCODONE OXYMORPHONE TRAMADOL	diphenoxylate heroin loperamide meperidine combinations - opioids plus acetaminophen and ASA	BUPRENORPHINE NALOXONE NALTREXONE	buprenorphine-naloxone butorphanol nalbuphine nalorphine nalmefene pentazocine

Learning Objectives

Physiology, pathophysiology and therapeutic actions

Describe the pharmacological effects and sites of action of the prototype opioid agonist morphine, and its utility in relieving different types of pain.

Discuss potential therapeutic actions of opioids aside from analgesia in CNS and other organ systems including cardiovascular, respiratory and GI.

Discuss the salient differences in pharmacology between morphine and each of the following agonists: meperidine, fentanyl, methadone, and oxycodone.

Mechanism of action

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

List the classes of opioid receptors and their associated functional roles. Explain the relevance of receptor heterodimers to opioid pharmacology.

Pharmacokinetics

Describe the pharmacokinetic processes affecting morphine, absorption, distribution, metabolism, excretion and how these are relevant to its therapeutic use. Describe the distribution of opioids in the body, including their ability to cross the blood-brain barrier and the placenta.

List opioid agonists that are metabolized to morphine and indicate the salient differences in their pharmacology from that of morphine.

Adverse effects, drug interactions and contraindications

List adverse effects of morphine on CNS, cardiovascular, GI-biliary, respiratory and genitourinary systems.

List and explain the major drug interactions of morphine.

List the contraindications for morphine and its surrogates.

Describe the characteristics of opioid tolerance and dependence, including the actions of morphine that do and do not show significant tolerance. Describe the opioid abstinence syndrome and how it differs from that for sedative-hypnotics.

Discuss abuse liability for opioids and how it differs among the various drugs.

Describe the signs and symptoms of morphine and heroin overdose and how they are managed.

Define precipitated abstinence and indicate under what circumstances it might occur following the clinical use of opioid analgesics or antagonists.

Therapeutic uses

Present the clinical indications for the opioids and opioid antagonists and explain the basis for their use.

Contrast the analgesic effects of morphine with those of the nonsteroidal antiinflammatory drugs, with those of antidepressants, and with those of carbamazepine and gabapentin, particularly in relation to the treatment of neuropathic pain conditions. Discuss the rationale for using mixtures of opioid analgesics and NSAIDS.

Discuss selection of appropriate therapeutic agents based on severity and type of pain; consider abuse potential versus therapeutic benefits of various opioids; and demonstrate awareness of legal and ethical issues in prescribing of opioids.

Explain how agonist-antagonists and partial agonists differ in their utility and adverse effect profile when compared to morphine.

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 opiate analgesics in oral and sublingual preparations permits opiate action, yet decreases abuse liability.

Explain the rationale for using methadone to treat heroin abusers. 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.

Discuss diversion and abuse of prescription opioids and approaches to minimize these occurrences.

Clinical Pharmacology

The drug of choice in this group remains as morphine. In patients with renal impairment, accumulation of morphine-6-glucuronide will contribute to the analgesic response. Under-dosing will aggravate smooth muscle spasm and actually increase the pain sensation, since this response occurs at lower morphine doses than that required for analgesia. Codeine is a prodrug. It has no analgesic efficacy and should never be used alone for significant pain relief. Deficiency in CYP2D6, whether genetic or induced by a competitive substrate drug, will decrease or eliminate the analgesic response after a codeine dose.

Fentanyl should only be used in morphine-tolerant patients. Its risk of abuse is considerably higher than with morphine. If analgesic therapy is switched from morphine to methadone, there will be a gap in analgesic coverage due to the slower onset of analgesic efficacy. In patients with heart disease or receiving concurrent drug therapy that prolongs the QTc interval, methadone is relatively contraindicated due to increased risk of cardiac arrhythmia induced by the methadone metabolite.

Tramadol has a slow onset of activity and should be considered as a secondary oral opioid analgesic treatment only for moderate to severe chronic pain. Oxycodone has a very high abuse potential and should be considered for pain management for short-term use only when CYP2D6 genetic deficiency is present or when concurrent drug therapy requires use of a CYP2D6 substrate.

Relevance

USMLE topic	**Principles of therapeutics**
Central and Peripheral Nervous System	Mechanisms of action and use of drugs for treatment of disorders of the nervous system- analgesics Treatment for substance abuse disorders

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 **Topic G** Diagnosis and management of patients with substance abuse problems

Antitussives	
Recommended Curriculum Equivalent: 0.5 hr	
Drug Classes and Drugs to consider	
Primary	Secondary
CODEINE DEXTROMETHORPHAN HYDROCODONE	guaifenesin
Learning Objectives	
Physiology, pathophysiology and therapeutic actions Describe the cough reflex and the sites of action of antitussive drugs, expectorants and mucolytic agents.	
Mechanism of action Discuss the mechanism of action of antitussive drugs.	
Relevance	
USMLE topic Respiratory System	**Principles of therapeutics** Mechanisms of action and use of drugs for treatment of disorders of the respiratory system - cough suppressants
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

Drugs Used in the Treatment of Motor Disorders and Centrally Acting Muscle Relaxants	
Recommended Curriculum Equivalent: 1 hr	
Drugs to consider	
Primary	Secondary
AMANTADINE BACLOFEN BENZTROPINE CARBIDOPA DANTROLENE DIAZEPAM DIPHENHYDRAMINE DOPAMINE ENTACAPONE L-DOPA PRAMIPEXOLE RASAGILINE ROPINEROLE SELEGILINE (deprenyl) TETRABENAZINE	apomorphine cyclobenzaprine propranolol tizanidine trihexyphenidyl
Learning Objectives	
Physiology, pathophysiology and therapeutic actions 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. Describe Huntington's Chorea and discuss drugs available for its treatment and their effectiveness. Discuss the pathophysiological basis of rigidity, spasticity, muscle spasm (if not previously discussed under motor dysfunction) and the classes of agents that are used to promote skeletal muscle relaxation (baclofen/GABAB receptors, tizanidine/alpha2 adrenergic receptors).	
Mechanism of action Describe the molecular mechanism of action of each primary drug.	
Adverse effects, drug interactions and contraindications Describe the similarities and differences in the adverse effect profiles of L-DOPA/carbidopa, COMT inhibitors, MAOB inhibitors and direct dopamine agonists.	

Therapeutic uses

Describe the rationale for the use of levodopa in Parkinson's disease and the rationale for its use in combination with peripheral L-amino acid decarboxylase inhibitor. Discuss how the drug combination alters levodopa's therapeutic and adverse effect profiles. Discuss the changes in control of symptoms by levodopa as disease progresses.

Discuss the use of other classes of drugs in treating Parkinson's disease: direct DA receptor agonists, anticholinergics, MAO inhibitors, COMT inhibitors, amantadine.

Discuss drugs that can cause parkinsonism and other movement disorders, and how these drug-induced disorders can be treated.

List drugs useful for treatment of spasticity and compare and contrast the mechanisms of action and adverse effects of benzodiazepines, baclofen, cyclobenzaprine and dantrolene when used for this purpose.

Explain the rationale for the use of dantrolene in malignant hyperthermia and neuroleptic malignant syndrome.

Clinical Pharmacology

There is significant potential for drug interaction among drugs in this group, especially carbidopa and L-DOPA when ingested with vitamins containing transition metals. The major problem with concurrent iron ingestion is reduced bioavailability of L-DOPA and carbidopa. This may be interpreted as disease progression rather than a drug – metal interaction. Drugs with anticholinergic properties may aggravate mental deficiencies (memory and cognition) such that the patient is prematurely institutionalized. Increased risk-taking on patients receiving high dose dopamine agonists (gambling, psychoses, etc. can occur).

Relevance

USMLE topic	**Principles of therapeutics**
Central & Peripheral Nervous System-Normal processes- motor system; basal ganglia; synthesis, storage, release reuptake and degradation of neurotransmitters **Abnormal Processes**- Parkinson disease, degenerative disorders	Antiparkinsonian drugs
AAMC Medical School Objectives Project Report X Patient Safety-Table 1	**Topic C:** Drug treatment of common conditions **Topic D**: Drug treatment of less common but severe conditions

Antiseizure drugs	
Recommended Curriculum Equivalent: 1 hr	
Drugs to consider	
Primary	Secondary
CARBAMAZEPINE DIAZEPAM ETHOSUXIMIDE LAMOTRIGINE LORAZEPAM PHENOBARBITAL PHENYTOIN TIAGABINE TOPIRAMATE VALPROIC ACID	clonazepam ezogabine fosphenytoin lacosamide levetiracetam perampanel pregabalin primidone rufinamide vigabatrin zonisamide
Learning Objectives	
Physiology, pathophysiology and therapeutic actions Describe the pathophysiology of seizures, and the types and prevalence of epilepsy. 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.	
Mechanism of action 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.	
Pharmacokinetics Describe the pharmacokinetic factors relevant to appropriate therapy with antiseizure drugs. Explain why the clearance of phenytoin changes with dose. Discuss the rationale for the common practice of monitoring plasma concentrations of many antiepileptic drugs.	
Adverse effects, drug interactions and contraindications List and describe the adverse and teratogenic effects of the major antiseizure drugs. 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.	
Therapeutic uses Describe the use of 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.	

Clinical Pharmacology

Differentiate between anticonvulsant and antiepilepsy actions on the basis of prophylaxis and acute therapy, and differentiate seizures from epilepsy.

Describe the role of anticonvulsant drug blood levels in the therapy of 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.

Relevance	
USMLE topic Central and Peripheral Nervous System	**Principles of therapeutics** Mechanisms of action and use of drugs for treatment of disorders of the nervous system Anticonvulsants
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

Drugs Used In The Treatment Of Mental Health Disorders

Drugs For The Treatment of Depression

Recommended Curriculum Equivalent: 1.5 hr

Drug Classes and Drugs to consider

Primary	Secondary
AMITRIPTYLINE BUPROPION DULOXETINE ESCITALOPRAM FLUOXETINE NORTRIPTYLINE PAROXETINE ST. JOHN'S WORT SELEGILINE SERTRALINE TRANYLCYPROMINE VENLAFAXINE	citalopram clomipramine desipramine fluvoxamine imipramine mirtazapine phenelzine trazodone

Learning Objectives

Physiology, pathophysiology and therapeutic actions

Describe the concept of behavioral affect, the current neurochemical and neurotrophic theories regarding affect and how it can be altered by drugs.

Define depression and list its symptoms, signs and causes.

Mechanism of action

List the major classes of antidepressant drugs and their primary cellular targets. (Tricyclic ADs, SSRIs, SNRIs, atypical antidepressants, and MAO inhibitors).

Discuss the mechanisms that could account for the delay in therapeutic actions of antidepressants.

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.

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 herbal antidepressants, such as St. John's wort.

Describe factors involved in the selection of appropriate drug(s) for a given patient.

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 tricyclic antidepressant toxicity and serotonin syndrome and their appropriate treatment.

Discuss possible drug interactions with St. John's wort.

Clinical Pharmacology

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.

Relevance

USMLE topic Central and Peripheral Nervous System	**Principles of therapeutics** Psychopharmacologic agents, drug induced adverse effects-CNS
AAMC Medical School Objectives **Project Report X Patient Safety-**Table 1	**Topic C** Drug treatment of common conditions

Drugs for treatment bipolar disorder

Drugs to consider

Primary	Secondary
CARBAMAZEPINE LAMOTRIGENE LITHIUM CARBONATE VALPROIC ACID ATYPICAL ANTIPSYCHOTICS: ARIPIPRAZOLE OLANZAPINE QUETIAPINE RISPERIDONE ZIPRASIDONE	clonazepam clozapine levetiracetam paliperidone primidone zonisamide

Learning Objectives

Physiology, pathophysiology and therapeutic actions

Describe the concept of behavioral affect, the current neurochemical theories regarding affect and how it can be altered by drugs.

Define bipolar disorder and its subtypes, and describe its signs and symptoms and its natural history. Describe manic episodes.

Mechanism of action

Describe the major theories explaining the presumed mechanisms of action of drugs useful for treating bipolar disorder (lithium, anticonvulsants, antipsychotics). List effects of lithium on CNS neurotransmitter systems.

Pharmacokinetics

Discuss the pharmacokinetics of lithium and its relationship to the following: alteration in dietary sodium, effects of exercise, use of diuretics, monitoring of plasma lithium levels, and treatment of lithium overdose.

Therapeutic uses

Contrast acute treatment of a manic episode and treatment designed to prevent bipolar cycling.

Discuss the use of antiseizure drugs for treatment of bipolar disorder, their advantages and disadvantages compared to lithium.

Adverse effects, drug interactions and contraindications

Differentiate adverse side effects of lithium from signs and symptoms of lithium overdose. Explain why there is a contraindication to the use of lithium in patients with impaired renal function or cardiovascular disease.

Clinical Pharmacology

See below: the treatment of psychoses

Relevance

USMLE topic	**Principles of therapeutics**
Central and Peripheral Nervous System	Psychopharmacologic agents, drug induced adverse effects-CNS
AAMC Medical School Objectives Project Report X Patient Safety-Table 1	**Topic C** Drug treatment of common conditions

Drugs for treatment of psychoses

Recommended Curriculum Equivalent: 1.5 hr

Drugs to consider

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

Learning Objectives

Physiology, pathophysiology and therapeutic actions

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.

Mechanism of action

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

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 Tourrette's syndrome.

Adverse effects, drug interactions and contraindications

Differentiate the side effect profile of low potency vs high potency classical (1st generation) antipsychotics. Provide an explanation for these differences.

Discuss the major area in which atypical (2nd and 3rd generation) antipsychotics' side effect profiles differ from those of classical (1st generation) antipsychotics, the nature of the differences and the mechanistic basis for the difference.

List the major side effects of each of the primary drugs.

Describe the time course, signs and symptoms of antipsychotic drug-induced dyskinesias (dystonia, akathesia, parkinsonism, tardive dyskinesia), and their management and treatment.

Describe neuroleptic malignant syndrome and its management and treatment.

Clinical Pharmacology

Care should be taken as metabolic disorders may be observEd with the second generation drugs, especially in patients with metabolic syndrome and/or a family history of diabetes.

Relevance

USMLE topic **Central and Peripheral Nervous System-** **Normal processes-** cognition **Abnormal Processes**- psychopathologic disorders; schizophrenia and other psychotic disorders	**Principles of therapeutics** Psychopharmacologic agents
AAMC Medical School Objectives **Project Report X Patient Safety-**Table 1	**Topic C:** Drug treatment of common conditions **Topic D**: Drug treatment of less common but severe conditions

Drugs For Treatment Anxiety And Sleep Disorders

Recommended Curriculum Equivalent: 2 hr

Drugs to consider

Primary	Secondary
ALPRAZOLAM	buspirone
DIAZEPAM	chloral hydrate
DULOXETINE	dexmedetomidine
ESCITALOPRAM	diphenhydramine
ESZOPICLONE	gamma-hydroxybutyrate
FLUMAZENIL (ANTAGONIST)	hydroxyzine
FLUOXETINE	lorazepam
LORAZEPAM	oxazepam
MIDAZOLAM	temazepam
RAMELTEON	zaleplon
SERTRALINE	
VENLAFAXINE	
ZOLPIDEM	

Learning Objectives

Physiology, pathophysiology and therapeutic actions

Briefly describe the concepts of sedation, hypnosis, anesthesia, coma. List and describe the stages of sleep.

Define anxiety, its relationship to the amygdala and differentiate the major anxiety disorders.

Discuss the $GABA_A$ receptor channel complex, the heterogeneity of its subunits and the physiological and therapeutic implications.

Describe translocator protein (18kD)-TSPO, its relationship to benzodiazepines and its possible relevance to drug treatment of anxiety.

Mechanism of action

Describe the effects of various sedative/hypnotic/anxiolytic drugs on $GABA_A$ function, their selectivity for different receptors with different subunit subtypes, and differences in their sites of action on the $GABA_A$ receptor channel complex.

Define inverse agonist at the $GABA_A$ receptor channel complex.

List sedatives, hypnotics and anxiolytics whose mechanism of action does not involve enhancement of $GABA_A$ function, and describe their molecular targets.

Adverse effects, drug interactions and contraindications

List the signs and symptoms of barbiturate and benzodiazepine overdose and its treatment. Explain how flumazenil might be used, and the rationale for its use.

Describe the interactions of the various classes of drugs used as hypnotics, sedatives and anxiolytics with other CNS depressants.

Compare the dependence liability, and withdrawal syndromes of the various classes of drugs used as hypnotics, sedatives and anxiolytics.

Discuss the interactions with alcohol.

Therapeutic uses

Compare and contrast the effects of barbiturates, benzodiazepines, and non-benzodiazepine agonists at the benzodiazepine site on induction and maintenance of sleep (including effects on sleep stages), and the adverse effects of these classes of drugs. Explain why drugs acting at the benzodiazepine receptor have virtually totally replaced barbiturates as hypnotics.

List the therapeutic uses of benzodiazepines, and prototypes for each use. Explain how pharmacokinetics of various benzodiazepines relates to their therapeutic utility.

Compare and contrast the hypnotic action of ramelteon and the anxiolytic action of buspirone with those of drugs acting at the benzodiazepine site of the GABAA receptor channel complex, and describe how their adverse effects including abuse potential differ.

Compare and contrast the sedative action of chloral hydrate, hydroxyzine and dexmedetomidine with those of drugs acting at the benzodiazepine site of the GABAA receptor channel complex, and describe how their adverse effects including abuse potential differ.

List drugs that are used for treating anxiety disorders other than generalized anxiety: panic disorder, obsessive-compulsive disorder, specific phobias. Can these drugs be used for generalized anxiety disorder as well?

Compare time course of anxiety relief with benzodiazepines vs SS/SNRIs.

Clinical Pharmacology

SSRIs are considered to have a higher benefit:risk ratio than the benzodiazepine or benzodiazepine-like drugs to treat anxiety states. Use as sedative-hypnotics of the benazodiazepine class is considerably abused. This therapeutic intervention is justified only for short-term administration. If benzodiazepines are to be used, intermediate-acting agents with primary elimination by Phase 2 drug metabolism are preferred due to reduced probability of a "hangover" effect. The only justifiable use of midazolam is part of a conscious sedation protocol prior to an uncomfortable diagnostic intervention.

Diazepam use in the elderly patient is problematic in that the terminal disposition half-life approximates age in the adult patient. However, this change is not related to a reduction in drug clearance but to an increase in apparent volume of distribution. Since its primary metabolite, desmethyldiazepam, has an even longer terminal half-life than diazepam, there is increased risk of hangover and reduced mental function with chronic use. When indicated, shorter acting benzodiazepines (lorazepam or oxazepam) are safer alternatives.

Relevance	
USMLE topic Central and Peripheral Nervous System	**Principles of therapeutics** Psychopharmacologic agents, drug induced adverse effects-CNS, hypnotic sedatives
AAMC Medical School Objectives **Project Report X Patient Safety-**Table 1	**Topic A** Factors that make each patient unique **Topic C** Drug treatment of common conditions

Stimulants and Anorexigenic Drugs	
Recommended Curriculum Equivalent: 0.5 hr	
Drugs to consider	
Primary agents	Secondary agents
AMPHETAMINES ATOMOXETINE CAFFEINE METHYLPHENIDATE MODAFINIL PHENTERMINE	ephedrine theophylline
Learning Objectives	
Physiology, pathophysiology and therapeutic actions Discuss the presumed physiological basis for the use of stimulants as anorexigenics, to enhance wakefulness, and in attention deficit hyperactivity disorder.	
Mechanism of action Describe the cellular mechanisms of action of the various stimulant drugs.	
Adverse effects, drug interactions and contraindications Discuss the adverse effects of stimulants with particular attention to cardiovascular problems and substance abuse.	
Therapeutic uses Discuss the use of stimulants for attention deficit hyperactivity disorder, narcolepsy, other sleep disorders, obesity, and apnea in the newborn. Discuss the limitations of using stimulants for weight loss.	
Clinical Pharmacology This should not be a first line treatment intervention for facilitation of weight loss due to increased cardiovascular risk in a population with a high likelihood of underlying cardiovascular disease. Tolerance and rebound weight gain upon cessation of use of these agents diminishes a rational justification of their use in management of obesity, given the risk of dependence and diversion for recreational use.	
Relevance	
USMLE topic Central and Peripheral Nervous System	**Principles of therapeutics** Mechanisms of action of drugs for treatment of disorders of the nervous system-stimulants, amphetamines
AAMC Medical School Objectives Project Report X Patient Safety-Table 1	**Topic C** Drug treatment of common conditions **Topic G** Diagnosis and management of patients with substance abuse problems

Drug and Substance Abuse

Recommended Curriculum Equivalent: 3 hr

Drug dependence, general principles

Learning Objectives

Physiology, pathophysiology and therapeutic actions

Define and differentiate tolerance to, physical dependence on and substance dependence (DSM-IVR) on drugs.

Discuss the roles of drug craving and reward vs. avoidance of withdrawal in initiation and maintenance of substance 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 and anxiolytics.

Drugs to consider - Psychostimulants

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

Learning Objectives

Mechanism of action

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

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.

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 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.

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.

Discuss current thoughts on potential treatments for stimulant drug dependence.

Clinical Pharmacology

The use of amphetamines with tricyclic antidepressants is contraindicated due to increased risk of cardiovascular morbidity and mortality.

Relevance

USMLE topic Central and Peripheral Nervous System	**Principles of therapeutics** Treatment for substance abuse disorders, amphetamines, psychopharmacological agents
AAMC Medical School Objectives Project Report X Patient Safety-Table 1	**Topic C** Drug treatment of common conditions **Topic G** Diagnosis and management of patients with substance abuse problems

Drugs to Consider - Ethanol and alcoholism	
Primary	Secondary
ETHANOL FOMEPIZOLE METHANOL NALTREXONE	acamprosate ethylene glycol topiramate

Learning Objectives

Physiology, pathophysiology and therapeutic actions

Describe the acute CNS actions of ethanol and discuss their relationship to blood alcohol levels.

Describe the effects of chronic alcohol on sleep.

Mechanism of action

Discuss current theories about the mechanism of action of alcohol in the CNS.

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.

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. 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.

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.

Clinical Pharmacology

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.

Relevance

USMLE topic	**Principles of therapeutics**
Central and Peripheral Nervous System	Treatment for substance abuse disorders, amphetamines, psychopharmacological agents
AAMC Medical School Objectives **Project Report X Patient Safety-**Table 1	**Topic C** Drug treatment of common conditions **Topic G** Diagnosis and management of patients with substance abuse problems

Drugs to Consider - Hallucinogens and Designer Drugs

Primary	Secondary
LYSERGIC ACID DIETHYLAMIDE (LSD) MDMA (methylene dioxymethamphetamine) MESCALINE PHENCYCLIDINE (PCP)	atropine bath salts (methylenedioxypyrovalerone) bufotenin ketamine psilocin salvia scopolamine

Learning Objectives

Physiology, pathophysiology and therapeutic actions

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.

Mechanism of action

List the hallucinogens with primary actions on $5HT_{2A}$ receptors, and those that are NMDA receptor antagonists, and muscarinic receptor antagonists and describe their mechanisms of action.

Pharmacokinetics

Describe how the pharmacokinetics of different drugs may influence their duration of action and their detection by screening tests for illicit drug use.

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.

Clinical Pharmacology

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.

Relevance

USMLE topic	**Principles of therapeutics**
Central and Peripheral Nervous System	Treatment for substance abuse disorders, amphetamines, psychopharmacological agents
AAMC Medical School Objectives **Project Report X Patient Safety-**Table 1	**Topic C** Drug treatment of common conditions **Topic G** Diagnosis and management of patients with substance abuse problems

Drugs to Consider - Marijuana

Primary	Secondary
DELTA-9-TETRAHYDROCANNABINOL (THC) DRONABINOL MARIJUANA	designer cannabinoids hashish K-2 nabilone spice

Learning Objectives

Physiology, pathophysiology and therapeutic actions

Discuss the endogenous cannabinoids, how they differ from classical neurotransmitters/neuromodulators, their receptors, and the current hypotheses about their functional roles.

List the psychological, physiological and pharmacologic effects of smoking marijuana; of taking dronabinol.

Compare and contrast patterns of marijuana use with that of other drugs of abuse.

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.

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.

Clinical Pharmacology

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.

Relevance

USMLE topic Central and Peripheral Nervous System	**Principles of therapeutics** Treatment for substance abuse disorders, amphetamines, psychopharmacological agents
AAMC Medical School Objectives Project Report X Patient Safety-Table 1	**Topic C** Drug treatment of common conditions **Topic G** Diagnosis and management of patients with substance abuse problems

Drugs to Consider - Inhalants/Organic solvents and gases

Primary	Secondary
GASOLINE	carbon tetrachloride fire extinguisher accelerants fluorocarbons gasoline glue nitrous oxide toluene

Learning Objectives

Adverse effects, drug interactions and contraindications

Discuss the epidemiology of abuse of inhalants.

Describe, in general terms, the effects of organic solvents and their toxicities

Drugs to Consider - Opioids

Agonists	Antagonists
BUPRENORPHINE BUPRENORPHINE/NALOXONE HEROIN METHADONE MORPHINE OXYCODONE (and abuse of prescribed opioids)	NALOXONE NALTREXONE

Learning Objectives

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.

Describe opioid tolerance and indicate differences in degree of tolerance achieved for various responses.

Discuss the opioid abstinence syndrome, list the signs and symptoms and compare and contrast these with withdrawal from CNS depressants including ethanol and benzodiazepines.

Therapeutic uses

Discuss treatment of opioid overdose in a chronic user of these drugs.

Discuss approaches used in drug formulation to limit the abuse and diversion of prescription opioids.

Describe the rationale and implementation of methadone maintenance for treatment of opioid abuse.

Explain the major differences between the use of methadone and buprenorphine for maintenance therapy. Explain why after initiating buprenorphine therapy, maintenance is commonly effected using a combination of buprenorphine and naloxone.

Discuss the rationale and limitations of the use of naltrexone for treating patients with opioid substance dependence.

Clinical Pharmacology

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 buprenoprhine 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.

There is no rationale for the use of heroin as an analgesic, since its therapeutic activity occurs as a result of its conversion to morphine.

Many jurisdictions are removing oxycodone from their formularies due to its enhanced risk:benefit profile and the availability of safer oral opioid analgesic formulations with a lesser tendency for abuse. Oxycodone use is probably only justified for short-term acute pain management as a second line drug, and only in patients with suppression of CYP2D6 activity.

Relevance

USMLE topic	**Principles of therapeutics**
Central and Peripheral Nervous System	Treatment for substance abuse disorders, amphetamines, psychopharmacological agents
AAMC Medical School Objectives Project Report X Patient Safety-Table 1	**Topic C** Drug treatment of common conditions **Topic G** Diagnosis and management of patients with substance abuse problems

Drugs to Consider – CNS general depressants

Primary	Secondary

BUTALBITAL DIAZEPAM ALPRAZOLAM FLUNITRAZEPAM	secobarbital zolpidem

Learning Objectives

Adverse effects, drug interactions and contraindications

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.

Therapeutic uses

Discuss treatment of barbiturate and benzodiazepine overdose in a chronic user of these drugs.

Clinical Pharmacology

Benzodiazepines 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.

Relevance

USMLE topic Central and Peripheral Nervous System	**Principles of therapeutics** Treatment for substance abuse disorders, amphetamines, psychopharmacological agents
AAMC Medical School Objectives Project Report X Patient Safety-Table 1	**Topic G** Diagnosis and management of patients with substance abuse problems

Drugs and the law

Therapeutic uses

Define the characteristics of drugs in each of the Drug Enforcement Administration classification of controlled substances into Schedules I, II, III, and IV, and give examples of some specific drugs that are included in each schedule. Discuss the ways in which this classification affects the clinical use of drugs.

Driving under the influence of alcohol, marijuana, others.

Relevance

USMLE topic Pharmacodynamic and Pharmacokinetic Processes – regulatory issues	**Principles of therapeutics**
AAMC Medical School Objectives Project Report X Patient Safety-Table 1	**Topic E** Rules and regulations that govern prescribing

Treatment of Alzheimer's Disease.	
Recommended Curriculum Equivalent: .3 hr	
Drugs to consider	
Primary	Secondary
DONEPEZIL GALANTAMINE MEMANTINE RIVASTIGMINE	
Learning Objectives	
Mechanism of action Discuss the drugs used for the treatment of Alzheimer's disease, their mechanisms of action, their efficacy and their adverse effects.	
Relevance	
USMLE topic **Central and Peripheral Nervous System-** **Normal processes-** cognition; memory; limbic system **Abnormal Processes**- degenerative disorders	**Principles of therapeutics** Drugs for dementia, Alzheimer type
AAMC Medical School Objectives **Project Report X Patient Safety**-Table 1	**Topic C:** Drug treatment of common conditions **Topic D:** Drug treatment of less common but severe conditions