Background on substance abuse (SA): leading cause of death, disability, and disease in United States; 25% of population has SA problem; speaker defines SA as "repeated, compulsive use of substance despite harm"

Origins of addiction: substances usurp brain systems that promote learning and repetition of behaviors; these reward systems reinforce certain actions (eg, eating, sexual intercourse for propagation of species) and typically describe relatively small mesolimbic dopaminergic pathway in brain

Mesolimbic dopaminergic pathway: also called mesocorticolimbic pathway (refers to connection with prefrontal cortex [PFC]); cell bodies in ventral tegmental area (VTA) project to area in basal medial forebrain (nucleus accumbens [NA]); terminals of these projections release dopamine (typically described as "neurotransmitter of reward") in NA; many other structures and neurotransmitters interact with and modulate reward pathways (eg, amygdala, PFC, hippocampus, structures in brainstem [eg, pedunculopontine nucleus])

Role of dopamine: all classes of addictive substances elevate levels of dopamine in critical synapses of NA through, eg, direct release from neuron terminals (seen with amphetamines), reuptake blockade (cocaine), excitation of cell bodies in VTA (nicotine), inhibition of inhibitory neurons in VTA (opioids), or release of endogenous opioid peptides (alcohol); kinetics — extremely important; short-acting, highly lipid-soluble substances with rapid uptake in brain typically produce larger changes in dopamine levels (neurochemical substrate of "rush" or "high" associated with SA); as such, short-acting substances generally more addictive, and promote frequent self-administration (repetitive reinforcement responsible for difficulties of smoking cessation)

Compensatory mechanisms in SA: triggered by repeated use of substances and associated disturbances in nervous system; adaptations to these disturbances manifest as tolerance (larger doses required to achieve similar effects) or sensitization (reverse of tolerance in which repeated administration leads to larger effects after abstinence; lasts ≥1 mo; most commonly occurs with stimulants, but seen with some effects of opioids); tolerance and sensitization can occur simultaneously with different effects of same substance (extremely dangerous)

Withdrawal syndrome: indicative of physical dependence; manifestation of body’s compensatory mechanisms in response to substances; symptoms virtually always occur in direction opposite to acute pharmacologic effects of substance (eg, withdrawal from substances associated with constipation produces diarrhea); as such, physicians can predict withdrawal symptoms based on type of SA; substances in same class have similar symptoms, but symptoms vary significantly between classes; severity and time course of withdrawal syndrome depends on pharmacologic history and pharmacokinetics of last substance taken; substituting long-acting agents for short-acting substances of abuse produces less intense but longer-lasting withdrawal, which patients find more tolerable (rationale for using, eg, methadone in opioid withdrawal, long-acting benzodiazepines [BZDs] in alcohol withdrawal)

Physical dependence: gradual change in motivation for SA; over time, individuals develop tolerance to euphoric effects of substance, but require continued use to prevent unpleasantness of withdrawal; drives substance use and complicates treatment of addiction; but does not cause addiction in and of itself; many individuals develop dependency after taking medication for chronic pain, but only 5% develop addiction after weaning; dependence and addiction can occur together or separately

Craving: cause of relapse; extremely difficult to treat; associated with numerous types of stimuli and cues typically difficult to extinguish; study (Childress et al, 1999) — used positron emission tomography to compare individuals with and without history of cocaine abuse during exposure to cocaine-related video; those with history of cocaine abuse experienced intense cravings and showed activity in brain regions activated by cocaine; thus, visual cues associated with SA can produce intense cravings even after years of abstinence; conclusions — cravings result from potent form of learning that occurs after repeated reinforcement of associations; cravings extremely difficult to extinguish; effects diminish over time, but often fail to disappear

Cues associated with withdrawal: can elicit conditioned withdrawal symptoms (qualitatively similar to genuine withdrawal, but less intense); patients may seek substances to eliminate withdrawal

Role of stress: different forms of stress can elicit craving and relapse (documented by many studies)

Substance use: similar substances or extremely low doses of abused substances may cause relapse

Managing cravings: strategies for effective management remain lacking; make patients aware of cravings, so they can prepare for or avoid relevant cues

Educational Objectives
The goal of this program is to improve knowledge of the neuroscience behind substance use and abuse. After hearing and assimilating this program, the clinician will be better able to:

1. Describe the evolutionary and physiologic origins of behaviors relevant to addiction.
2. Explain how addiction, dependency, tolerance, and withdrawal develop from substance use.
4. Identify how specific substances produce and reinforce self-administration.

Faculty Disclosure
In adherence to ACCME Standards for Commercial Support, Audio-Digest requires all faculty and members of the planning committee to disclose relevant financial relationships within the past 12 months that might create any personal conflicts of interest. Any identified conflicts were resolved to ensure that this educational activity promotes quality in health care and not a proprietary business or commercial interest. For this program, Dr. Glick and the planning committee reported nothing to disclose.
Amphetamines:
dextroamphetamine, amphetamine and dextroamphetamine mixed salts (Adderall), and dextromethamphetamine have similar pharmacology despite different indications; methylenedioxymethamphetamine (MDMA; also known as, eg, “ecstasy,” “Molly,” “Mandy”), methylenedioxymethamphetamine, and paramethoxymethamphetamine primarily used as drugs of abuse (due to hallucinogenic properties) and potently release serotonin (classic amphetamines cause more potent release of dopamine); *mechanism of action*—reverse activity of dopamine transporters to tremendously increase levels of dopamine in synaptic space; while high doses of cocaine can elevate synaptic levels of dopamine by 6- to 7-fold, reversing dopamine transporters elevates these levels by 10- to 15-fold

Cocaine: vasoconstriction after insufflation may cause epistaxis and holes in nasal septum (uniquely indicative of cocaine abuse); partially metabolized into benzoylecgonine (possible cause of delayed strokes and seizures seen after cocaine abuse); using cocaine with alcohol forms cocaethylene (described as most addictive substance); combining cocaine and alcohol estimated to increase cocaine-related risk for sudden death by ≈18-fold; blocks reuptake sites on dopamine receptor, leaving higher concentrations of dopamine available to activate receptors (similar effects seen with noradrenaline and serotonin); effects on dopamine primarily responsible for addiction

Nicotine: often considered as addiction, nicotine is rapidly absorbed; smokers generally attempt to maintain narrow range of nicotine levels in brain; animals shown to self-administer nicotine (along with all other substances associated with addiction in humans); metabolized more slowly in women (relative to men); bind to nicotinic receptors (acetylcholine acts as endogenous agonist; ion receptor found in many different varieties with 5 subunits; present throughout body)

### Sedatives

**Epidemiology of alcohol binge drinking:** peaks at 20 to 29 yr of age (similar to other forms of SA); after this decade, behavior often ceases or diminishes due to increased physical illness (alcoholism reduces lifespan by 15-30 yr)

**Pharmacokinetics of alcohol:** concentration of alcohol in blood depends on many variables (eg, alcohol content of beverages, rate of imbibing, consumption of food, gastric emptying rate, rate of metabolism); these variations confound generalizations about consumption, but general guidelines specify ≤2 drinks daily for men and ≤1 drink daily for women as safe limits; metabolized in liver and stomach (relatively minor, but more significant in men); genetic influences—some blacks have gene for faster metabolism of alcohol (via more active form of alcohol dehydrogenase); many Asians have gene that impairs metabolism of aldehyde dehydrogenase, leading to accumulation of acetaldehyde when drinking alcohol (sufficient quantities produce flushing, headaches, difficulty breathing, and chest pain); individuals homozygous for this gene do not develop alcoholism; given equivalent doses of alcohol, women have higher blood levels of alcohol compared to men

**Effects of alcohol:** enhances effects of γ-aminobutyric acid (GABA; primary inhibitory neurotransmitter); stimulates and blocks particular types of acetylcholine receptors (eg, nicotinic receptors); blocks N-methyl-D-aspartate (NMDA) receptors (excitatory glutamate receptor); elevates levels of dopamine (probably mediated by release of endogenous opioid peptides and their effects on short GABA-ergic interneurons in VTA); efficacy of naltrexone (opioid antagonist) evidences role of opioids in alcoholism

**Barbiturates:** differ in duration of action; pharmacologically similar to other general sedatives, and thus show cross-tolerance and cross-dependence with, eg, alcohol, BZDs

**Functioning of GABA A receptors:** chloride ions to flow through open channels, resulting in inhibitory influences on nearby neurons; barbiturates generally enhance actions of GABA by causing chloride channels to stay open for longer durations; however, at extremely high doses, barbiturates can open ion channels without GABA; thus, increasing doses of barbiturates have no upper limit to their effects, and can easily lead to overdose or death; BZDs also enhance effects of GABA, but cannot open ion channels themselves, and thus have asymptote that limits their effects; BZDs, barbiturates, and anticonvulsants have different binding sites in GABA receptor subcomplex with slightly different modes of action, but have similar net effects on functioning of GABA

**Subtypes and subunits:** ≥2 types of GABA A receptors exist, comprised of 5 α-subunits (depending on types of subunits present, receptors may mediate different effects (sedative, ataxic, and anesthetic vs antianxiolytic and anticonvulsant effects); BZDs have almost equal affinity for both types of GABA A receptors, whereas zolpidem (eg, Ambien, Edluar, Intermezzo), eszopiclone (Lunesta), and zaleplon (Sonata) have preferential activity at receptors that mediate sedative effects (ie, only minimally anxiolytic)

**Stimulants**

**Amphetamines:** dextroamphetamine, amphetamine and dextroamphetamine mixed salts (Adderall), and dextromethamphetamine have similar pharmacology despite different indications; methylenedioxymethamphetamine (MDMA; also known as, eg, “ecstasy,” “Molly,” “Mandy”), methylenedioxymethamphetamine, and paramethoxymethamphetamine primarily used as drugs of abuse (due to hallucinogenic properties) and potently release serotonin (classic amphetamines cause more potent release of dopamine); *mechanism of action*—reverse activity of dopamine transporters to tremendously increase levels of dopamine in synaptic space; while high doses of cocaine can elevate synaptic levels of dopamine by 6- to 7-fold, reversing dopamine transporters elevates these levels by 10- to 15-fold

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### Opioids

**Prescription opioids:** abuse viewed by speaker as “epidemic” (over past 10 yr, attributed overdose deaths and prescriptions have increased 4-fold)

**Pharmacodynamics:** bind to μ (μ), κ (κ), and δ opioid receptors; ≥95% of available opioids work exclusively at μ receptor; all subtypes produce analgesic effects; activation of κ receptor can produce hallucinogenic effects

Heroin: prodrug that does not bind directly to receptors; highly lipophilic and reaches brain extremely rapidly; short-acting properties (relative to morphine) promote addiction

Morphine: slow uptake due to relatively poor lipid solubility

**Oxycodone:** typical μ-opioid receptor agonist; popular in SA due to inappropriate prescribing and advertising

**Hydrocodone:** recently rescheduled and restricted to prevent abuse; typical opioid; has effects qualitatively similar to oxycodone (depending on dose)

**Meperidine:** has unique effects attributed to metabolite (normeperidine) with stimulant properties; only opioid associated with pupil dilation (all others cause constriction); may produce convulsions at high doses (problematic in patients whose impaired renal function or phenobarbital use for seizures promotes buildup of normeperidine); used only with caution in proper context; less effect on gut and uterus compared to other opioids

**Meptidine:** maintenance treatment for opioid dependence and withdrawal; increasingly used for pain (and thus increasingly associated with overdose); long duration of action, but analgesic effects may only last 6 to 8 hr

### Hallucinogens

**Lysergic acid diethylamide:** not addictive (possibly due to rapid tolerance); partial agonist of serotonin 2A receptor

**Phencyclidine (PCP):** emergency department (ED) visits related to use of PCP increased 10-fold since 2011; common adulterant in other substances (often without user’s knowledge); only hallucinogen routinely associated with auditory hallucinations; can induce psychotomimetic syndrome (difficult to distinguish from idiopathic psychosis in ED); life threatening (may cause convulsions and respiratory arrest); blocks NMDA receptors; inhibits dopamine reuptake (promotes addiction); described as most dangerous substance

**Methylenedioxymethamphetamine:** ED visits related to use of MDMA increased 3-fold in past 10 yr; taken orally; releases serotonin and dopamine; numerous studies found MDMA damages neurons that contain serotonin and reduces serotonin uptake sites
Marijuana: tetrahydrocannabinol (THC; active ingredient) content has increased from ≈1% in 1970s to average of 10% to 12%, and thus associated dangers increased; ED visits related to use of marijuana increased 4-fold between 2002 and 2011; although THC has half-life of ≈60 hr, effects of smoking marijuana dissipate after 1 to 2 hr (suggests rapid form of acute tolerance); accumulates in fat and brain (may explain “reverse tolerance” and delayed effects reported by users); effects mediated by cannabinoid receptors CB1 (most prevalent in brain; mediates most effects associated with use of marijuana) and CB2 (located in periphery; mediates immunosuppressive effects); THC impairs short-term memory (30-60 sec range) and sense of time; analgesia occurs as variable and unpredictable phenomenon; impairs motor coordination at high doses, and driving at lower doses (due to impaired judgment)

Inhalants: extremely harmful chemicals; typically abused by adolescents, commonly in southwestern United States; rapid uptake into brain; short half-lives; cause serious damage to multiple organs; typically sedative and enhance effects of GABA, and can be hallucinogenic

Anabolic steroids: typically used for perceived effects on muscle mass; diffuse into cells, bind with intracellular receptors, and drug-receptor complexes attach to DNA to alter transcription and eventual protein synthesis; causes diverse effects throughout body (reversible or irreversible depending on various factors); may cause withdrawal syndrome associated with depression and suicide

“Designer” drugs: derivatives or structural analogues of illegal substances not covered by federal law; legal control likely to require continual passing of new laws; synthetic cannabinoids — typically far more potent (and dangerous) than THC; most forms recently scheduled and controlled; Salvinorin A — extracted from Mexican plant; most potent known hallucinogenic (possibly via effects on κ-opioid receptors); “bath salts” — typically derived from cathinone (natural plant-based stimulant; similar to amphetamines); methylenedioxypyrovalerone and mephedrone most prevalent

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Suggested Reading
1. Every type of addictive substance raises levels of dopamine in critical synapses of the:
   (A) Ventral tegmental area
   (B) Nucleus accumbens
   (C) Prefrontal cortex
   (D) Hippocampus

2. Sensitization to the effects of a substance most often occurs with:
   (A) Sedatives
   (B) Stimulants
   (C) Opioids
   (D) Hallucinogens

3. Symptoms of withdrawal virtually always occur in the direction opposite to the acute pharmacologic effects of a substance.
   (A) True
   (B) False

4. Alcohol binge drinking and other forms of substance use typically peak at:
   (A) Adolescence
   (B) 15 to 21 yr of age
   (C) 20 to 29 yr of age
   (D) 25 to 35 yr of age

5. Alcohol is known to block:
   (A) γ-aminobutyric acid (GABA) receptors
   (B) N-methyl-D-Aspartate receptors
   (C) Dopamine receptors
   (D) Noradrenaline receptors

6. Which of the following medications is capable of opening chloride ion channels without the presence of GABA, thus creating a significant risk for overdose and death?
   (A) Alprazolam
   (B) Zolpidem
   (C) Diazepam
   (D) Phenobarbital

7. Amphetamines increase levels of dopamine in the brain by:
   (A) Blocking the reuptake of dopamine
   (B) Exciting cell bodies in the ventral tegmental area
   (C) Reversing the action of dopamine transporters
   (D) Releasing endogenous opioid peptides

8. Which of the following acts as the endogenous agonist of nicotinic receptors?
   (A) Acetylcholine
   (B) Glutamate
   (C) N-methyl-D-aspartate
   (D) GABA

9. Which of the following opioids causes pupil dilation instead of constriction, due to its unique stimulating effects?
   (A) Oxycodone
   (B) Hydrocodone
   (C) Meperidine
   (D) Methadone

10. Which of the following is the only hallucinogen routinely associated with audio hallucinations?
    (A) Lysergic acid diethylamide
    (B) Phencyclidine
    (C) Marijuana
    (D) Salvinorin A