





The Science of Addiction

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Disclaimer: no conflicts of interest

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LEARNING OBJECTIVES

At the completion of this presentation the attendees will be able to:

- 1. Describe the neurobiological basis of addiction
- 2. Summarize the epidemiology and trends in substance use and substance use disorders in the US
- 3. Describe the greatest challenges facing the US today and how research is attempting to address them
- 4. Understand the important role of policy in prevention and treatment of substance use and SUD

Drug Addiction

- Compulsive drug use
- Gene/environment
- Preventable, treatable
- Chronic, relapsing
- Affects organs including the brain
- Usually starts during adolescence

Disease

STAGES OF THE ADDICTION CYCLE



BINGE AND INTOXICATION

- All drugs of abuse activate dopamine in reward region
- Link to preceding environmental stimuli
- Cue-induced anticipatory dopamine release
- Conditioned response trigger craving (even after drug use stops)



WITHDRAWAL AND NEGATIVE AFFECT

- Reduced dopamine levels -> diminished reward system
- Increased stress/negative emotions ("anti-reward" system)
- Shift from desire for pleasure to avoiding distress



PREOCCUPATION AND ANTICIPATION

- Prefrontal changes to executive processes
- Impaired self-regulation, decision making
- Difficulty resisting strong urges
- Impulsiveness
- Craving



Reinforcement: Neurochemical systems



Neurobiological Substrates for the Acute Reinforcing Effects of Drugs of Abuse

Drug of Abuse	Neurotransmitter	Site
Cocaine and amphetamines	Dopamine γ -Aminobutyric acid	Nucleus accumbens Amygdala
Opioids	Opioid peptides Dopamine Endocannabinoids	Nucleus accumbens Ventral tegmental area
Nicotine	Dopamine γ-Aminobutyric acid Opioid peptides	Nucleus accumbens Ventral tegmental area Amygdala
Δ^9 -Tetrahydrocannabinol	Endocannabinoids Opioid peptides Dopamine	Nucleus accumbens Ventral tegmental area
Alcohol	Dopamine Opioid peptides γ-Aminobutyric acid Glutamate Endocannabinoids	Nucleus accumbens Ventral tegmental area Amygdala



Regulation of gene expression by drugs of abuse (Nestler, 2001)

Epidemiology: Past Year Illicit Drug Use Among People 12 y.o. and older, 2021





https://www.samhsa.gov/data/sites/default/files/reports/rpt39443/2021NSDUHFFRRev010323.pdf

. Past Year <u>Substance Use Disorder</u> (DSM5) Among People Aged 12 or Older; 2021



¹Includes marijuana, cocaine, heroin, hallucinogens, inhalants, methamphetamine, and prescription psychotherapeutic drugs

² Includes data from all past year users of the specific prescription drug

³ It does not add up because some people had multiple stimulant use disorders.

NSDUH, SAMHSA, 2021

2022-2023: Provisional* Drug Overdose Deaths 12-months ending in select months

	ALL DRUGS	HEROIN	NAT & SEMI SYNTHETIC	METHADONE	SYNTHETIC OPIOIDS (mainly illicit fentanyl)	COCAINE	OTHER PSYCHO- STIMULANTS (mainly meth)
7/2022*	109,416	7,190	12,707	3,443	74,048	26,989	34,724
1/2023*	110,784	5,753	11,917	3,362	76,438	28,607	35,766
7/2023*	111,964	4,768	11,076	3 <i>,</i> 405	78,287	30,290	36,937
Percent Change 7/22-7/23	2.3%	-33.7%	-12.8%	-1.1%	5.7%	12.2%	6.4%

*NCHS Provisional drug-involved overdose death counts are <u>PREDICTED VALUES</u>, 12 months ending in select months. The numbers for 2022 differ from final data in slide 1 because provisional data includes all deaths that occurred in the US including foreign residents. Final data through 2021 on slide 1 is limited to deaths in US residents. <u>https://www.cdc.gov/nchs/nvss/vsrr/drug-overdose-data.htm</u>



Source: The Multiple Cause of Death data are produced by the Division of Vital Statistics, National Center for Health Statistics (NCHS), Centers for Disease Control and Prevention (CDC), United States Department of Health and Human Services (US DHHS).

110,469 drug overdose deaths between March/2022 and March/2023

Drug Overdose Death Rates by Race/Ethnicity



Prevention	 Alternatives to pain management Increased awareness about OD risk factors Mental health parity laws 	ے م
Treatment	 Increased access to medication for opioid use disorder Increased workforce trained to provide services Access to medications for OUD inside jails Integration into primary care 	
Recovery	 Increased access to recovery housing Funding for peer drop in centers Increase number of Peer Support Specialists 	
Emergency Intervention	 Naloxone administration to individuals who overdose Leave behind naloxone to individuals who overdose Emergency department warm handoffs to treatment agencies 	
Harm Reduction	 Syringe exchange programs Naloxone distribution to people who use drugs Education about safer-use practices 	

FORTIFIED SCHOOLS **PREVENTION IS KEY**

SOCIAL ACTIVITIES

PARTICIPATION IN SPORTS, ARTS

INFORMATION DISSEMINATION

ON N

NARCAN FOR EVERYBODY

SOCIAL JUSTICE

MENTAL HEALTH

STRUCTURAL RACISM

COMMON SENSE GUI REGULATIONS

HOMELESSNESS

STIGMA

PAST YEAR SUBSTANCE USE DISORDER (SUD) AND PERCEIVED NEED FOR TREATMENT (2021)

People Aged 12 or Older



People with a Past Year Illicit Drug or Alcohol Use Disorder Who Did Not Receive Substance Use Treatment at a Specialty Facility in the Past Year



- Note: The estimated numbers of people with substance use disorders are not mutually exclusive because people could have use disorders for more than one substance.
- ¹ Includes data from all past year users of marijuana, cocaine, heroin, hallucinogens, inhalants, methamphetamine, and prescription psychotherapeutic drugs (i.e., pain relievers, tranquilizers, stimulants, or sedatives).
- ² Includes data from all past year users of the specific prescription drug.

40.7 Million People with an Illicit Drug or Alcohol Use Disorder Who Did Not Receive Substance Use Treatment at a Specialty Facility



FDA-Approved Medications

- Opioid Use Disorder
 - Methadone
 - Buprenorphine
 - Buprenorphine/naloxone
 - Weekly, monthly, 6-month buprenorphine
- Opioid Use Relapse Prevention
 - Oral and depot naltrexone
- Opioid Withdrawal
 - Lofexidine
- Opioid Overdose
 - Naloxone
 - Nalmefene

NO FDA Approved Medications

Stimulant Use Disorder Cocaine Methamphetamine Prescription stimulants Cannabis Use Disorder

EMERGING TREATMENTS

- Longer acting medications (new formulations): methadone, buprenorphine, naltrexone
- Biologics: Vaccines, monoclonal antibodies
- Digital Therapeutics: apps and other interactive modalities
- Devices: TDCS (transcranial direct current stimulation); Focused Ultrasound; TMS (transcranial magnetic stimulation)
- Other target behaviors: Sleep; Overdose prevention (i.e. reverse respiratory depression)
- Deep brain stimulation: Nucleus Accumbens
- Psychedelics (Alcohol, nicotine, comorbid depression)



Opioid Overdose - Treatment









Harm Reduction Research Network

Purpose: Increase our understanding of effectiveness, implementation, and impact of existing and new harm reduction strategies

Novel harm reduction for approaches s	or and modes of service delivery	and addressing barriers	Reaching understudied populations	Coordination Center – 4 cores
 Community drug checking Overdose prevention centers Meth sobering center Contingency management 	Emergency department Mobile apps Hotline Text messages Mail delivery Secondary distribution Remote lockboxes	 Limited access Not using naloxone when it is available Burnout & trauma from responding to overdose State-level policy barriers 	 Racial/ethnic minority groups Women Rural communities People who use stimulants 	 Communication and Coordination Data Harmonization and Methodology Community and Stakeholder Engagement Dissemination and Translation



Fentanyl: Research Gaps

- Re-narcotization
- Respiratory depression
- Wooden chest syndrome
- Its analogs
- Naloxone-precipitated withdrawal
- Reduction of risk
- "Naloxone-resistant"



Promising Med Targets for OUDs



Koob GF, Volkow ND. Neuropsychopharmacol Rev, 2010

Mechanisms to reduce stress-induced drug seeking

- Kappa Opioid Receptor Antagonists
- OX-1 Receptor Antagonists
- NOP Receptor Agonists
- a2-Adrenergic Receptor Agonists
- PDE7 Inhibitors

Mechanisms to reduce cue-induced

drug seeking

- D3 Receptor Antagonists
- OX-1 Receptor Antagonists
- 5-HT2C Receptor Agonists
- 5-HT2A Receptor Inverse Agonists
- mGluR2 Positive Allosteric Modulators
- 5-HT6 Receptor Inhibitors
- PDE7 Inhibitors

Addiction Is a Developmental Disease



9 out of 10 people who meet the clinical criteria for substance use disorders involving nicotine, alcohol or other drugs began smoking, or drinking or using other drugs started using alcohol and marijuana before they turned 2

ource: "Adolescent Substance Abuse: America's #1 Public Health Problem" ational Center on Addiction and Substance Abuse at Columbia University

Past Year Drug Use



NSDUH, SAMHSA, 2021

Substance Use Disorder



NSDUH, SAMHSA, 2021

Adolescent Brain Cognitive Development Study

96.3 Percent Retained









ABCD 5.1 Data Released

through the NIMH Data Archive

- New Data Dictionary Explorer (<u>https://data-dict.abcdstudy.org/?</u>)
- New ABCD Wiki Release Notes (<u>https://wiki.abcdstudy.org/</u>)

HEALthy Brain and Child Development Study



New Threats

Nitazenes

- Developed in the 1950s as opioid analgesics
- Never approved to market
- High potency (more potent than fentanyl).
- Often found mixed with fentanyl or other agents
- Challenge since there is little experience
- Public health efforts are needed to better inform street drug consumers, first responders, healthcare professionals, and the general public about these drugs that are infiltrating the recreational drug supply.



Xylazine

- Potent analgesic
- For horses and Cervidae
- Alpha 2 agonist
- Severe hypotension, CNS depressant
- Vasoconstriction
- Used to prolong fentanyl effects
- Skin burns





Recovery is **Possible**



Normal Control



µmol/100g/min Control Subject **METH Use** METH Use (30 y/o, Female) (27 y/o, Female) (27 y/o, Female) 3 months detox 13 months detox Source: Volkow, ND et al., Journal of Neuroscience 2001

(1 month detox) (14 months detox)

METH User

ml/gm

Improvements in Brain Metabolism with **Prolonged Abstinence** from Methamphetamine Use

G-J Wang et al., Am J Psychiatry 2001

Take Home Key Messages



- Multiple neurobiological models of addiction
- Drug use, SUDs, and overdose are significant public problems
- Multiple public health efforts that involve prevention, treatment, rehabilitation, harm reduction, and research
- NIDA is supporting research on all aspects of SUDs
- Treatment research is a high priority
- Emphasis on drug use among adolescents
- New drugs are emerging in the illicit market (e.g., xylazine, nitazenes)
- Recovery is possible and can be evidenced with neuroimaging studies



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• <u>https://nida.nih.gov/about-nida/organization/divisions/division-</u> <u>therapeutics-medical-consequences-dtmc</u>